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Drinking Water and Health

Part II
Chapters 6 and 7

The National Research Council

A Report of the Safe Drinking Water Committee

Advisory Center on Toxicology

Assembly of Life Sciences

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Drinking Water and Health

Part II
Chapters 6 and 7

A Report of the Safe Drinking Water Committee
Advisory Center on Toxicology Assembly of Life Sciences
National Research Council

NATIONAL ACADEMY OF SCIENCES
Washington, D. C. 1977

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the Committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, The National Academy of Engineering, and the Institute of Medicine.

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Chapter VI

ORGANIC SOLUTES

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INTRODUCTION

SELECTION OF AGENTS. In selecting agents to be included in the organic contaminants section of this report, a number of tabulations of organic contaminants detected in drinking water were examined. From these lists, agents were selected which have been reported to be present in one or more drinking water supplies at relatively high concentrations and for which there were data to suggest toxicity in man or animals. Also included were several agents which exhibit a structural relationship to other compounds for which toxicity data were available, and all of the agents listed in the current interim standards as well as those specific compounds listed in the Federal Register of December 24, 1975. A total of 298 volatile organic compounds were considered and 74 of these were selected for evaluation.

Similar criteria were used to select the organic pesticides for inclusion in this report. Several additional agents were added after examination of the usage patterns for all major types of organic pesticides as well as a number of agents which were considered to be potential contaminants of drinking water supplies because of the large quantities produced. A total of 55 organic pesticides were selected for evaluation.

EVALUATION OF AGENT TOXICITY. A critical review of the available literature on the toxicology of each agent (or group of related agents) was carried out as the first stage in the evaluation process. Although the primary focus in these reviews was on carcinogenesis and other chronic toxic effects, test results and data on teratogenesis, mutagenesis, reproductive effects, metabolism, acute toxicity, and other types of studies were included when available. Information on the current production, manufacturing methods and environmental distribution was included for some pesticides and other organic compounds.

In the second stage of the evaluation process, both the quantity and quality of the information in each of the critical reviews was considered to determine whether the data would permit sound professional judgements to be made regarding carcinogenicity or the establishment of a maximum no-observed-adverse-effect level.

Compounds which were considered to be known or suspected carcinogens were evaluated (See Chapter II of this report) to obtain a dose-related risk assessment analysis for each agent. The limitations which are inherent in the extrapolation of high-dose animal bioassay data to low-dose human exposure situations and the difficulty of making predictions for species which may have different metabolic rates and pathways for handling carcinogens and/or different target organ responses are recognized. Such risk assessment and extrapolation procedures are further compromised by the limited information which is available concerning the mechanisms by which these agents act (initiators, promotors, modifiers etc.) and the almost total lack of data regarding the potential synergistic and antagonistic interactions of these agents with each other and with other environmental agents. Despite these and other uncertainties, the risk estimate approach has been adopted as the basis for analysing the critical review carcinogenesis data rather than the "safety factor approach."

After a substance had been identified as a carcinogen, the risk to man was expressed as the probability that cancer would be produced by continued daily ingestion over a 70 year lifetime of 1 liter of water containing a standard quantity (1 μg/liter) of the substance in question. Estimates expressed in this form may then be used to calculate risk due to the concentrations actually found in drinking water and the daily consumption.

To make such estimates from the results of animal feeding studes two steps are necessary. The first involves conversion of the standard human dose to the physiologically equivalent dose in the animal. This was performed on the basis of relative surface area (details are given in Hoel *et al.*, 1975, Chap. II). The second step requires use of a risk model relating dose to effect. The model used for this purpose is

$$P(d) = 1 - e^{-(\lambda_0 + \lambda_1 d + \lambda_2 d^2 + \ldots + \lambda_K d^K)}$$

where P(d) is the lifetime probability that dose d (total daily intake) will produce cancer,

K = the number of events in the carcinogenic process and $\lambda_0, \lambda_1, \lambda_2$...etc. are nonnegative parameters (See Ch. II) At low doses, the higher order terms in d^2, d^3, etc. may be neglected and

$$P(d) = 1 - e^{-(\lambda_0 + \lambda_1 d)} \cong \lambda_0 + \lambda_1 d$$

λ_0 representing the background rate. When two or more sets of results of lifetime animal feeding studies were available, experimental values of P(d), the fraction of test animals developing cancer, and d, the total daily dose, were fitted to the equation to determine how many of the terms $\lambda_1 d, \lambda_2 d^2$, etc., were necessary to give the best fit. Corresponding values of λ_1 or λ_1 and λ_2, etc. were used to calculate P(d) for the low dose of interest, namely the animal dose that was physiologically equivalent to the standard dose for man. If the animal experiments involved only one dose level, the $\lambda_1 d$ term, alone, was used in the calculation. Upper confidence limits in the estimated low dose risk were also calculated by use of maximum likelihood theory (Guess and Crump, 1976, Chap II), and these values were tabulated. Since the animal data were obtained from lifetime feeding studies, the risk estimates calculated from them for the low doses that were estimated to be physiologically equivalent to the human dose were taken to represent the lifetime risks for man. The background rate, obtained from the cancer incidence in the control groups of experimental animals and represented by the parameter λ_0, was excluded from the tabulated values of P(d), which therefore represent the incremental risks due to ingestion of the compounds in water.

It was felt that predictions which are risk-related provide a more meaningful first approximation of hazard than safety-related predictions. The risk estimate approach may provide unique advantages for other areas of toxicological evaluation such as mutagenesis and it is recommended that the usefulness of this program be evaluated as a new and novel predictive tool in toxicology.

For agents which were not considered to be known or suspected carcinogens and for which there were adequate toxicity data from prolonged ingestion studies in man and/or animals, the more traditional approach was utilized of combining the maximum dose producing no-observed adverse effects with an uncertainty (risk) factor to calculate an ADI (acceptable daily intake). Several alternative terms, other than ADI, were considered, but it was concluded that the introduction of new terms might well lead to confusion and that the use of a widely recognized and generally acceptable term would be preferable for this report. The ADI has been used previously as an internationally established standard for the toxicologic evaluation of food additives and contaminants and the concept is applicable to other ingestion exposure situations. The ADI represents an empirically derived value which reflects a particular combination of knowledge and uncertainty concerning the relative risk of a chemical. The uncertainty factors used to calculate ADI values in this report represent the level of confidence which was judged to be justified on the basis of the animal and human toxicity data. All calculations for an ADI were based on chronic feeding studies, but other considerations, e.g., mutagenicity, teratogenicity, and lack of sex and strain information, influenced the choice of the uncertainty factor. ADI values were not calculated for agents where the data were considered to be inadequate.

Since the calculation of the ADI values is based on the total amount of a chemical which is ingested, the ADI values calculated in this report do not represent a safe level for drinking water. However, a suggested no-anticipated adverse effect level has been calculated for these chemicals in drinking water using two hypothetical exposure situations (where water constitutes 1% and 20% of the total intake of the agent) and similar calculations can readily be made for other exposure situations.

CONCLUSIONS. The organic contaminants which have been identified in drinking water constitute a small percentage of the total organic matter present in water. Although approximately 90% of the volatile organic compounds in drinking water have been identified and quantified, these represent no more than 10% of the total organic material. Of the non-volatile organic compounds comprising the remaining 90% of the total organic matter in water, only 5 to 10% have been identified. From the 74 non-pesticide organic compounds and 55 organic pesticides selected for study, 22 have been identified as known or suspected carcinogens, 46 as having sufficient toxicity data to permit the calculation of an ADI value or a suggested no-adverse effect level for drinking water, 6 as mutagens, and 7 as teratogens. There were 61 agents for which the toxicity data were judged to be inadequate for establishing any recommendations. (See Tables VI-63 and 64 in Summary of Organic Solutes.)

It is evident that this effort constitutes only the beginning of a very large task. However, in preparing these reports and recommendations, an attempt has been made to utilize procedures which will enable subsequent efforts to be focused on adding to and updating rather than on redoing the task. Also identified are certain priorities for the selection of agents to be studied and the research needs in toxicology and epidemiology to facilitate the evaluation of the potential health hazards associated with organic agents which are or may be present in our drinking water supplies.

B. PESTICIDES

a: Herbicides
1. Chlorophenoxys

2,4-D

I. INTRODUCTION

2,4-D, or 2,4-dichlorophenoxyacetic acid, was introduced as a plant growth-regulator in 1942 (EPA, 1974b). It is registered in the United States as an herbicide for control of broadleaf plants and as a plant growth-regulator. Domestic use of 2,4-D is estimated at 40-50 million pounds a year, approximately 84% of which is used agriculturally and about 16% nonagriculturally (mainly for forest brush control).

2,4-D is produced commercially by chlorination of phenol to form 2,4-dichlorophenol, which reacts with monochloroacetic acid to form 2,4-D (EPA, 1974b). Commercial 2,4-D formulations are generally composed of the salts or esters (ethyl, isopropyl, butyl, amyl, heptyl, octyl etc.) of the acid. Analysis of 28 samples of technical 2,4-D by gas chromatography showed that hexachlorodioxins were, from all manufacturing sources, present in only one sample, at less than 10 ppm (Woolson *et al.*, 1972). The dioxin most likely to be formed, 2,7-dichlorodibenzo-p-dioxin, was not found. The major impurity in technical 2,4-D was identified as *bis*-(2,4-dichlorophenoxy)methane, at 30 ppm (Huston, 1972).

The solubility of 2,4-D in water is 540 ppm at 20°C; its major breakdown product, 2,4-dichlorophenol, is soluble at 4,500 ppm (EPA, 1974b). The 2,4-D salts are in general highly soluble, but the esters are much less soluble.

2,4-D is chemically quite stable, but its esters are rapidly hydrolyzed to the free acid. Microbial degradation of 2,4-D contributed to its rapid breakdown (half-time, 1 week) in water (USEPA, 1974b). When exposed to sunlight or ultraviolet irradiation, aqueous 2,4-D solutions decompose to 2,4-dichlorophenol, 4-chlorocatechol, 2-hydroxy-4-chlorophenoxyacetic acid, 1,2,4-benzene triol, and polymeric humic acids. The overall breakdown rate of 2,4-D in aqueous solution is fairly high, and 2,4-dichlorophenol is even more photolabile. Most 2,4-D residues are retained in the soil, where breakdown usually occurs within 6 weeks.

Between 1964 and 1970, only 56 samples of food were found to be contaminated with 2,4-D; the concentrations detected were 0.021-0.16 ppm (USEPA, 1974b). Residues were found in 1% or less of dairy products, oils, fats and shortening, and fruit, in 1.6% of leafy vegetables, and in 22.1% of sugar and adjuncts.

2,4-D is found in water (Manigold and Schulze, 1969). Concentrations as high as 70 ppb have been detected in Oregon streams after aerial application to forest land (Hiatt, 1976). 2,4-D was detected in raw water at 0.05 µg/liter, in Lafayette, Indiana (USEPA, 1975i). The EPA has set an interim standard for 2,4-D in finished water of 0.1 mg/liter (USEPA, 1975i).

II. METABOLISM

When 2,4-D labeled with carbon-14 was administered orally to sheep, 96% of the dose was excreted unchanged in the urine in 72 h, slightly less than 1.4% in the feces (Clark et al., 1964). When adult sheep and cattle were fed 2,4-D in the diet for 28 days at up to 2,000 ppm, the kidney contained the highest and the liver somewhat lower concentrations of 2,4-D and its breakdown product 2,4-dichlorophenol (Clark et al., 1975). Withdrawal from treatment for 7 days resulted in almost complete elimination of 2,4-D and its major metabolite from the tissues.

In rats that received 1-10 mg of 2,4-D, there was almost complete excretion in the urine and feces in 48 h; at higher doses, some accumulation occurred in tissues (Khanna and Fang, 1966).

After subcutaneous injection of 2,4-D and its butyl and isooctyl esters into mice at 100 mg/kg, the esters were eliminated rapidly, and only 5-10% of the 2,4-D remained after 1 day (USEPA, 1974b). No 2,4-dichlorophenol was detected in extracts of the treated mice.

In feeding studies of 2,4-D with dairy cows and steers, unchanged 2,4-D was found only in the urine (Bache et al., 1964a, b; Gutenmann et al., 1963a, b; Lisk et al., 1963). Other studies (Burchfield and Storrs, 1961; Klingman et al., 1966) demonstrated that 2,4-D was eliminated in the milk of cows maintained in pastures treated with 2,4-D or its butyl or isooctyl ester.

The pharmacokinetic profile of 2,4-D has been determined in five male human volunteers (Sauerhoff et al., 1976). After ingestion of a single 5-mg/kg oral dose, 2,4-D was eliminated from plasma in an apparent first-order process with an average half-life of 11.7 h. All subjects excreted 2,4-D in the urine with an average half-life of 17.7 h, mainly as free 2,4-D (82.3%), with a smaller amount excreted as a 2,4-D conjugate (12.8%).

III. HEALTH ASPECTS

A. Observations in Man

A 46-year-old male farmer accidentally ingested a 2,4-D formulation; the dose was estimated to contain 2,4-D at 100 mg/kg, S-ethyldipropylthiocarbamate at 230 mg/kg, and epichlorohydrin at 2.3 mg/kg (Berwick, 1970). The clinical picture was indicative of 2,4-D poisoning with symptoms including fibrillary twitching and muscular paralysis. Serum glutamic oxalacetic transaminase, glutamic pyruvic transaminase, lactic dehydrogenase, aldolase and creatine phosphate were increased, and both hemoglobinuria and myoglobinuria were observed. After recovery of the patient, there was also a 4-month loss of sexual potency.

In testing 2,4-D for possible use in disseminated coccidiomycosis, 18 intravenous doses were administered to a patient over a 33-day period, with no observed side effect (Seabury, 1963). The dosage was 15 mg/kg for the last 12 doses, except that the eighteenth was increased to 37 mg/kg. Following the nineteenth and final dose of 67 mg/kg, the patient exhibited fibrillary twitching and general hyporeflexia. The patient later died, apparently owing to the disease.

After a 23-year-old man used 2,4-D in suicide, the lethal dose was estimated to be over 90 mg/kg (Nielsen et al., 1965).

Assouly (1951) is reported to have taken 2,4-D daily at 8 mg/kg for 3 weeks without harmful effects. Data from Dow Chemical Co. (Johnson, 1971) on 220 workers exposed to 2,4-D at 0.43-0.57 mg/kg per day over a period of 0.5-22 years showed no significant differences from data on an unexposed human population.

B. Observations in Other Species

Acute Effects. The acute toxicity of 2,4-D is moderate in a number of animal species, with LD_{50} values of 100-541 mg/kg for rats, mice, guinea pigs, chicks, and dogs (Drill and Hiratzka, 1953; Rowe and Hymas, 1954). Salts and esters of 2,4-D show an even lower degree of acute toxicity.

The acute oral toxicity of the major 2,4-D breakdown product 2,4-dichlorophenol is 580 and 1,625 mg/kg for the rat and the mouse, respectively (Toxic Substances List, 1974).

Subchronic and Chronic Effects. Young adult female rats were given oral doses of 2,4-D in olive oil at 0, 3, 10, 30, 100, and 300 mg/kg five times a week for 4 weeks (Rowe and Hymas, 1954).

No adverse effects were noted at 30 mg/kg and below but depressed growth rates, liver pathology, and gastrointestinal irritation occurred at 300 mg/kg. In another experiment (Rowe and Hymas, 1954), depressed growth, liver pathology, mortalities, and increased liver/body weight ratios were observed in rats fed 1,000 ppm 2,4-D for 113 days.

2,4-D was administered orally to dogs at dosage levels of 0, 2, 5, 10, and 20 mg/kg five days a week for 13 weeks (Drill and Hiratzka, 1953). Three of four animals receiving 20 mg/kg dose died within 49 days. These animals showed a definite decrease in the percentage of lympocytes in the peripheral blood. The surviving animals in all groups did not show any hematological abnormalities.

Dietary levels of 0, 5, 25, 125, 625 and 1,250 ppm technical grade 2,4-D were fed to female and male Osborne-Mendel rats for two years (Hansen et al., 1971). No significant effects were observed on growth, survival rate, organ weights, or hematologic parameters. There was also no elevated incidence of tumors over that seen in controls.

In a parallel study (Hansen et al., 1971), groups of 6 - 8 month old beagle dogs received 0, 10, 50, 100 and 500 ppm of technical 2,4-D for 2 years. No 2,4-D related effects were noted. None of the lesions observed in the 30 dogs were believed related to the treatment.

The no-adverse effect level of 2,4-D in the dog has been established at 8.0 mg/kg/day (Lehman, 1965).

Mutagenicity. 2,4-D was unable to induce point mutations in four microbial systems (Andersen et al., 1971) and showed no activity in Drosophila (Vogel and Chandler, 1974).

Saccharomyces cerevisiae strain D4 (5×10^8) was treated with 2 ml of an aqueous 2,4-D suspension (trade name, U46D-Fluid) (Siebert and Lemperle, 1974). The mitotic gene conversion frequency of the ade 2 locus was increased 5-fold above control values; that of the trp 5 locus was increased 6-fold above control values.

Carcinogenicity. Studies on the in vitro and in vivo effect of 2,4-D on the growth of Ehrlich ascites tumor in BALB/c mice showed that the herbicide was inhibitory at 45 mg/kg or more (Walker et al., 1972). There was no significant increase in the incidence of tumors in various mouse strains initially given 2,4-D or its esters at 46.4 mg/kg/day orally on days 7-28 followed by dietary feeding up to 323 ppm for 18 months (USEPA, 1976b). In another study, mice that received 2,4-D orally for their life span showed no increased incidence of tumor formation (Vettorazzi, 1975b).

A study (Arkhipov and Kozlova, 1974) reported that two rats developed fibroadenoma and one hemangioma 27-33 months after receiving one-tenth the LD_{50} of the amine salt of 2,4-D. Administration of 0.1 the LD_{50} dose of the amine salt orally or subcutaneously to mice produced no tumors after 33 months. The herbicide, however, had a cocarcinogenic effect in mice when it was applied to the skin with 3-methylcholanthrene. DNA synthesis was increased, and there was a loss of cell differentiation in cultured chicken muscle after treatment with high concentrations of 2,4-D (Haag *et al.*, 1975).

2,4-Dichlorophenol has not been tested for carcinogenicity alone (USEPA, 1974b), but it is an initiator for skin carcinogenesis (Boutwell and Bosch, 1959).

Reproduction. In a three-generation, six-litter Osborne-Mendel rat reproduction study, no deleterious effects due to technical 2,4-D at dietary doses of 100 or 500 ppm were observed (Hansen *et al.*, 1971). At 1,500 ppm, however, 2,4-D, although affecting neither fertility of either sex nor litter size, sharply reduced the percentage of pups that survived to weaning and the weights of the weanlings.

Teratogenicity. In studies of CD-1 mice, Courtney (cited in EPA, 1974b) found that 2,4-D at 221 mg/kg per day increased fetal mortality, but produced no cleft palates. Various 2,4-D esters (isopropyl ester at 147 mg/kg/day, n-butyl ester at 155 mg/kg/day, and isooctyl ester at 186 mg/kg/day) had no effect on the incidence of cleft palate or fetal mortality, but did affect fetal weight. A significant increase in cleft palate was found, however, after administration of the propylene glycol butyl ether ester at 195 mg/kg/day.

A statistically significant increase in the proportion of abnormal fetuses was reported in mice that received maximally tolerated subcutaneous doses of the isooctyl ester, and two isopropyl esters of 2,4-D (130, 100, and 94 µg/kg, respectively), in dimethyl sulfoxide (DMSO) solution (Mrak, 1969). DMSO itself, however, is a teratogen (Caujolle *et al.*, 1967).

Bage *et al.* (1973) observed teratogenic and embryotoxic effects in NMRI mice that received 50- or 110-mg/kg injections of 2,4-D on days 6-14 of gestation.

Pregnant rats were treated orally with 2,4-D at 12.5, 25, 50, 75, and 87.5 mg/kg/day (maximal tolerated dose) or equimolar doses of propylene glycol butyl ether ester of 2,4-D up to 142 mg/kg/day or isooctyl ester of 2,4-D up to 131 mg/kg/day on days 6-15 of gestation (Schwetz et al., 1971). Fetotoxic responses were seen at the high dosages, but teratogenic effects were not seen at any dosage. The authors suggested that the no-adverse effect dosage of 2,4-D (or the molar equivalent, in the case of the esters) was 25 mg/kg/day.

Prenatal studies on 2,4-D in Wistar rats showed that it induced fetotoxic effects and an increased incidence of skeletal anomalies after single oral doses of 100-150 mg/kg/day on days 6-15 of gestation (Khera and McKinley, 1972). At the highest dosage of 150 mg/kg/day, the isooctyl ester, and butyl ester, and butoxyethynol and dimethylamine salts of 2,4-D were all associated with significantly increased teratologic incidence. The butyl and isooctyl esters also tended to decrease fetal weight. At a lower dosage, 2,4-D, and its salts and esters induced no apparent harmful effects.

Pregnant hamsters received technical 2,4-D (three samples) at 20, 40, 60, and 100 mg/kg/day orally on days 6-10 of gestation (Collins and Williams, 1971). Terata were produced occasionally with 2,4-D, and the fetal viability per litter decreased; but neither effect was clearly dose-related. The lowest dose causing fetal anomalies with the three technical 2,4-D samples was 60 mg/kg/day.

IV. CONCLUSIONS AND RECOMMENDATIONS

The acute toxicity of 2,4-D is moderate. No adverse effect doses for 2,4-D were up to 62.5 mg/kg/day and 10 mg/kg/day in rats and dogs respectively. Based on these data, an ADI was calculated at 0.0125 mg/kg/day. The available data on subchronic and chronic toxicity and calculations of ADI are summarized in Table VI-1.

The acceptable daily intake of 2,4-D has been established at 0.1 mg/kg by FAO/WHO. On the basis of electron-capture gas chromatography, the detection limit for 2,4-D in water is 1 ppb.

There are substantial disagreements in the results of subchronic and chronic toxicity studies with 2,4-D, perhaps reflecting the use of different formulations or preparations. In view of these deficiencies and the variability of the results, additional, properly constituted toxicity studies should be undertaken.

TABLE VI-1: Summary of Toxicity Data for 2,4-D

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Dog	13 weeks	0-16 mg/kg/day 5 animals per group	7.4 mg/kg/day	no toxic effect	Drill and Hiratzka, 1953
Dog			8.0 mg/kg/day	no toxic effect	Lehman, 1965
Dog	2 years	0-500 ppm in diet 6 animals/group	500 ppm (12.5 mg/kg/day)[c,d]	no toxic effect	Hansen *et al.*, 1971
Rat	4 weeks	0-300 mg/kg/day 5-6 females/group	30 mg/kg/day	no toxic effect	Rowe and Hymas, 1954
Rat	days 6-15 of gestation	0-87.5 mg/kg/day 15-19 females per group	25 mg/kg/day	no feto-toxic effect	Schwetz *et al.*, 1971
Rat	2 years	0-1,250 in diet 50 animals per group	1,250 ppm (62.5 mg/kg/day)[d]	no toxic effect	Hansen *et al.*, 1971

Using an uncertainty factor of 1000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{12.5}{1000} = 0.0125 \text{ mg/kg/day (ADI)},\ 0.0125 \times 70^{a} \times 0.1^{b} = 0.09 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse effect level.

[d] Assume weight of rat = 0.4 kg and of dog = 10 kg; assume average daily food consumption of rat = 0.02 kg and of dog = 0.25 kg.

2,4,5-T and TCDD

I. INTRODUCTION

2,4,5-T, or 2,4,5-trichlorophenoxyacetic acid, was introduced in 1944 as a translocated, selective herbicide; it is applied after emergence and is effective on woody plants (Spencer, 1973; Thomson, 1975; Weed Society of America, 1974). 2,4,5-T and its salts and esters are registered in the United States for noncrop areas, especially on woody plants, pastures, and rangelands (Thomson, 1975). It is still used for weed control on rice and sugar cane. The 1971 U.S. production of 2,4,5-T and its derivatives is estimated at 6 million pounds (NAS, 1975).

2,4,5-T is produced by interaction of 2,4,5-trichlorophenol with the sodium salt of monochloroacetic acid (Spencer, 1973). Esters of 2,4,5-T are synthesized by esterification of the acid with the appropriate alkyl alcohol. The solubility of 2,4,5-T in water at 25°C is 278 ppm (Spencer, 1973); 2,4,5-T salts are water-soluble, but the esters are generally insoluble.

2,4,5-T is more stable than 2,4-D. The 2,4,5-T esters are rapidly hydrolyzed after spraying and the 2,4,5-T is then further decomposed by bacterial action. The major product of 2,4,5-T photodecomposition was 2,4,5-trichlorophenol (Crosby and Wong, 1973). Other products identified including 4,6-dichlororesorcinol, 4-chlororesorcinol, 2,5-dichlorophenol, 2-hydroxy-4,5-dichlorophenoxyacetic acid, and 2,4,5-trichloroanisole.

2,4,5-T is rapidly adsorbed onto particulate matter or broken down in water. Nevertheless, in the period 1965-1968, 2,4,5-T was detected in surface water at concentrations of 0.01-0.07 ppb (Johnson, 1971).

Very little 2,4,5-T was found in food in analyses of raw agricultural products and in the Market Basket Survey samples (Advisory Committee on 2,4,5-T, 1971). Of about 10,000 food and feed samples examined from 1964 to 1969, only 25 contained trace amounts of 2,4,5-T (less than 0.1 ppm), and only two contained measurable amounts (0.19 and 0.29 ppm). The Advisory Committee on 2,4,5-T (1971) concluded that 2,4,5-T did not accumulate in the biosphere and that the risk of human exposure in food, air, or water was negligible.

Technical 2,4,5-T contains traces of the highly toxic compound 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as an impurity (Advisory Committee on 2,4,5-T, 1971). In addition, about 0.0002% of 2,4,5-T is converted to TCDD when wood or brush containing 2,4,5-T is burned (Stehl and Lamparski, 1977). 2,4,5-

T preparations formerly contained TCDD at 1-80 ppm, a concentration sufficiently high to cause chloracne in industrial workers and to impart specific toxic properties that were characteristic of TCDD to the 2,4,5-T. It has not been feasible to eliminate TCDD completely from technical 2,4,5-T, but it is now reported to be present in commercial 2,4,5-T at less than 0.1 ppm (Advisory Committee on 2,4,5-T, 1971).

Water transport of TCDD is limited, because it is soluble in water at only 0.2 ppb (Advisory Committee on 2,4,5-T, 1971). TCDD is decomposed photochemically (Crosby *et al.*, 1971, 1973). It is firmly bound to soil, where it tends to persist for more than a year.

The Advisory Committee on 2,4,5-T (1971) concluded that there was no indication that TCDD accumulates in air, water, or plants, although it might accumulate in soils after heavy applications of 2,4,5-T.

II. METABOLISM

2,4,5-T is readily absorbed and rapidly excreted by animals, including man. Rats and pigs given single 100-mg/kg doses of the amine salt of 2,4,5-T showed plasma half-lives of 3 and 10 h, respectively (Erne, 1966a,b). There was little buildup in tissues, and the compound was excreted mainly in the urine.

During the first 24 h, 75% of the radioactivity was excreted in the urine and 0.2% in the feces of female Wistar rats that had been given 0.17, 4.1, and 41 mg/kg orally of ^{14}C-carbonyl labelled 2,4,5-T (Fang *et al.*, 1973). No ^{14}C was found in the expired air. Radioactivity was detected in all tissues, with the highest concentration appearing in the kidneys. Radioactivity was detected in the fetuses of pregnant rats, and the average half-life of 2,4,5-T radioactivity in the organs was 3.4 h for the adult rats and 97 h for the newborns.

The half-life values for the clearance of carbon-14 activity from the plasma of rats given single oral doses of ^{14}C-carboxyl-labeled 2,4,5-T at 5, 50, 100, and 200 mg/kg were 4.7, 4.2, 19.4, and 25.2 h, respectively (Piper *et al.*, 1973). Half-lives for elimination from the body were 13.6, 13.1, 19.3, and 28.9 h, respectively. Cumulative excretion over a 144 h period was 82.6, 92.0, 78.3, and 68.4% of the administered dose of 5, 50, 100, and 200 mg/kg, respectively. A small amount of an unidentified metabolite was detected in the urine at the two highest dosages.

In dogs given ^{14}C-carboxyl-labeled 2,4,5-T at 5 mg/kg, half-life values for clearance and from the body were 77.0 and 86.6 h, respectively (Piper *et al.*, 1973). This low rate of clearance may explain why 2,4,5-T is more toxic in dogs than in rats. Some 42% of the dose was elimated in the urine and 20% in the feces over a 9-day period. Three unidentified metabolites were found in the urine.

Five human male volunteers ingested a single 5-mg/kg dose of 2,4,5-T that contained TCDD at less than 0.05 ppm (Gehring *et al.*, 1973). Clearance of 2,4,5-T from the plasma and its excretion from the body occurred with a half-life of 23.1 h. Essentially all the 2,4,5-T was absorbed and excreted unchanged in the urine.

After oral administration of 2,4,5-T to rats and mice, the unchanged herbicide was the main excretion product in the urine (Grunow *et al.*, 1971; Grunow and Bohme, 1974). Other urinary metabolites were identified as the glycine and taurine conjugates of 2,4,5-T as well as 2,4,5-trichlorophenol. In addition to 2,4,5-T, 2,4,5-trichlorophenol residues appeared in the tissues of sheep and cattle fed the herbicide (Clark *et al.*, 1975).

After a single oral 1-μg/kg dose of ^{14}C-labeled TCDD in rats, radioactivity was found only in the feces, and the half-life of radioactivity in the body was 30.4 days (Rose *et al.*, 1976). Liver and fat contained carbon-14 concentrations ten times greater than those in other tissues examined 22 days after ingestion. The carbon-14 activity in the liver was associated with TCDD. TCDD reaches essentially steady-state concentrations after 90 days of daily exposure, and that period is independent of the administered dose for the range of 0.01-1.0 μg/kg/day. TCDD is excreted primarily via the feces; only 4.5% of the radioactivity from an oral dose of labeled TCDD was eliminated in urine during 21 days (Allen *et al.*, 1975). A large percentage of the radioactivity remaining in the body at the end of this period was in the liver--over 90% within the microsomal fraction. TCDD apparently undergoes little if any metabolism (Fullerton *et al.*, 1974).

III. HEALTH ASPECTS

A. Observations in Man

Data compiled by Dow Chemical Company showed that 126 manufacturing personnel exposed to 2,4,5-T at an estimated 1.6-8.1 mg/day (0.02-0.12 mg/kg/day) for periods of up to 3 years developed no herbicide-related illness (Advisory Committee on 2,4,5-T, 1971).

The results were entirely different in another plant, where the 2,4,5-T produced contained a high proportion of TCDD (Bleiberg *et al.*, 1964; Poland *et al.*, 1971); 18% of the men suffered moderate to severe chloracne, and several cases of porphyria were found. Chromosomal analysis of 52 workers exposed for various periods up to 569 days to 2,4,5-T (containing TCDD at <1 ppm) at 1.6-3.1 mg/day failed to show any abnormalities (Johnson, 1971).

B. Observations in Other Species

Acute Effects. Rowe and Hymas (1954) reviewed the early toxicologic information on 2,4,5-T and concluded that the oral LD_{50}s for male rats, male mice, guinea pigs, and chicks were 500, 389, 381, and 310 mg/kg, respectively. They also concluded that the acute toxicity of the butyl, isopropyl, and amyl esters of 2,4,5-T in the rat, guinea pig, and chicken was all greater than that listed above. Johnson (1971) has reported acute oral toxicity studies with commercial 2,4,5-T in which the LD_{50} were 500 mg/kg in the rat and 380 mg/kg in the guinea pig. The oral LD_{50} of 2,4,5-T in the dog was greater than 100 mg/kg (Drill and Hiratzka, 1953). It is not clear, however, how much TCDD contamination was present in the 2,4,5-T used in these studies.

TCDD is extremely toxic, as shown by oral LD_{50} values ranging between 0.6 and 115 µg/kg for several animal species (Schwetz, 1973). In the rat, oral LD_{50}s were 22 and 45 µg/kg for males and females, respectively, with death occurring 9-47 days after administration. The guinea pig was much more sensitive, with LD_{50} values of 0.6 and 2.1 µg/kg for males and females, respectively. Limited data showed that dogs were less sensitive to TCDD than rabbits. The LD_{50} for TCDD was 114 µg/kg in 3-month-old male C57Bl/6 mice (Vos et al., 1974).

Rats that received a single 100 µg/kg dose of TCDD showed 43% mortality, severe liver damage, thymic atrophy, and icterus (Gupta et al., 1973). Animals given 50 and 25 µg/kg showed severe and moderate thymic atrophy and liver damage. In guinea pigs given 3.0 µg/kg, there was a 90% mortality, the appearance of hemorrhage, atrophy of adrenal zona glomerulosa, and depletion of lymphoid organs.

Female rats given a single oral dose of TCDD of up to 300 µg/kg showed delayed mortality over a 90-day period (Greig et al., 1973). It was not possible to estimate an LD_{50} value, because of the irregular distribution of deaths in the treatment groups. The mean time to death was 40.4 days for animals that received 200 µg/kg. The animals lost weight, and significant changes in liver constitution appeared after 3 days. The liver showed pathologic changes in later periods, particularly the formation of multinucleate parenchymal cells. Gastric hemorrhage and jaundice also were common. Pericardial edema and death in chickens followed a single oral dose of 25-50 µg/kg .

Subchronic and Chronic Effects. In work by Dow Chemical Co. reported in 1961 (Advisory Committee on 2,4,5-T, 1971), the monopropylene, dipropylene, and tripropylene glycol butyl ether esters of 2,4,5-T were administered orally to rats over a 90-day period at up to 186 mg of 2,4,5-T/kg/day. At the highest dosage and at 62 mg/kg/day, toxicity was observed, but no deleterious effects were seen at dosages of 18.6 and 6.2 mg/kg/day.

Ninety-day feeding studies with 2,4,5-T containing TCDD at 0.5 ppm were reported in 1970 by McCollister and Kociba (Advisory Committee on 2,4,5-T, 1971). The herbicide was administered to rats at 3, 10, 30, and 100 mg/kg/day. No adverse effects were observed in animals that received 30 mg/kg/day or less, but growth was decreased and changes in serum enzyme concentrations were observed at 100 mg/kg/day.

Maternal mice given four to eight doses of a technical preparation containing 97.9% 2,4,5-T at 120 mg/kg/day often developed myocardial lesions, hypocellularity of the bone marrow, and depletion of lymphocytes in the thymus, spleen, or lymph nodes (Highman and Schumacher, 1976). To determine whether the previous effects were due to 2,4,5-T alone or to TCDD, further studies were conducted in which female mice received, on nine successive days, either technical 2,4,5-T or a purified preparation of 2,4,5-T orally at 60 and 120 mg/kg/day (Highman *et al.*, 1975). All mice given 60 mg/kg and some of which given 120 mg/kg appeared normal at sacrifice and showed little or no pathologic change. Mice susceptible to 120 mg/kg became ill or moribund after one to eight doses, and few survived 11 days; 36 of 66 moribund mice given the technical and 23 of 33 given the purified 2,4,5-T had myocardial lesions, and more showed lesions in other organs. These findings support the view that the lesions are due primarily to 2,4,5-T, rather than to dioxins in the technical preparation.

Drill and Hiratzka (1953) found no adverse effects in dogs that were fed 2,4,5-T five times a week for 90 days at 2.5 and 10 mg/kg. Four dogs treated at 20 mg/kg died during the experiment.

A study was conducted in which rats received TCDD at 0.001, 0.01, 0.1, or 1.0 μg/kg 5 days a week for 13 weeks (Kociba *et al.*, 1976). No discernible adverse effect occurred in rats that received 0.01 or 0.001 μg/kg TCDD but 0.1 μg/kg caused degenerative changes in the liver and thymus, porphyria, altered serum enzyme concentrations, and loss in body weight.

Four month-old male C57Bl/6 mice received TCDD at 0.2, 1.0, 5.0, and 25 μg/kg orally once a week for 2 or 6 weeks (Vos *et al.*, 1974). Some deaths and growth retardation occurred in the 25 μg/kg group. Significantly increased liver and decreased thymus weights were found in the 1-, 5-, and 25-μg/kg groups. Total neutrophils were increased significantly, whereas hemoglobin values and mean corpuscular hemoglobin concentrations were decreased significantly after six doses of 25 μg/kg. Total serum proteins and globulins also were decreased. TCDD was porphyrogenic, probably as a result of liver damage. At the lowest dosage, 0.2 μg/kg, slight but consistent centrilobular fatty changes were observed in the liver.

Gross pathologic and histopathologic examinations were performed on rats, guinea pigs, and mice that received daily or weekly treatments with TCDD for up to 8 weeks (Gupta _et al._, 1973). In rats and guinea pigs the dose ranged from a no-adverse effect dose to one that produced death. Lymphoid organs, primarily the thymus, were consistently affected over a wide range of dosage in all species examined. Thymic atrophy is a very sensitive index of TCDD exposure. The severity of liver pathology was quite variable between species, the most severe effects being found in the rat and the degenerative and necrotic changes being markedly lower in the guinea pig and mouse.

Surprisingly, no adequate chronic toxicity tests have been conducted with 2,4,5-T. In a long-term exposure study, mice received 21.5 mg/kg daily from the first through the fourth week and thereafter received 60 ppm (equivalent to 9 mg/kg) in the diet until 18 months had elapsed (Innes _et al._, 1969). It is presumed that all animals survived the test period, but this was not stated.

Dogs and rats are said to tolerate oral intake of 2,4,5-T at 10 mg/kg/day for long periods (Advisory Committee on 2,4,5-T, 1971).

Mutagenicity. 2,4,5-T was unable to induce point mutations in four different microbial systems (Anderson _et al._, 1972). Buselmaier _et al._ (1972) conducted host-mediated assays in NMRI mice with mutants of _Salmonella typhimurium_ and _Serratia marcescens_ and produced no mutagenic effect with 2,4,5-T at 500 mg/kg or the n-butyl ester of 2,4,5-T at 1,000 mg/kg. These investigators also reported on dominant lethal tests in NMRI mice; no adverse effect was noted with 2,4,5-T at 1,000 mg/kg. The herbicide had no mutagenic effect in _Drosophila melanogaster_ (Vogel and Chandler, 1974). Inhibition of mitosis and the development of abnormalities in plants by 2,4,5-T formulations have been shown to be due to TCDD contamination (Jackson, 1972).

A great number of chromosomal abnormalities were induced in bone marrow cells of gerbils given 2,4,5-T at 150, 250, or 350 mg/kg (Majumdar and Hall, 1973).

Khera and Ruddick (1973) conducted dominant lethal tests in which male Wistar rats received TCDD orally at 4 or 8 µg/kg/day for seven days. Later reproduction studies failed to show any dominant lethal mutations during 35 days after treatment. TCDD is apparently negative in a mutagenicity test with *Salmonella typhimurium* (Fullerton *et al.*, 1976). It also appears to have no potential for producing chromosomal aberrations in the bone marrow of male rats (Green and Moreland, 1975).

Although many reports indicate that TCDD is not mutagenic, Hussain *et al.* (1972) reported that TCDD is strongly mutagenic in various bacterial systems.

Carcinogenicity. No significant increase in the incidence of tumors was seen in two strains of mice that received 2,4,5-T (containing TCDD at approximately 30 ppm) at 21.5 mg/kg per day from the end of the first week through the fourth week and at 60 ppm in the diet thereafter until the age of 18 months (Innes *et al.*, 1969).

In one experiment, intraperitoneal injections of TCDD at 1 and 10 mg/kg induced liver lesions that "appeared to be malignant" (Buu-Hoi *et al.*, 1972). The significance of this report is highly questionable, because the lowest TCDD dose was almost 50 times greater than the oral LD_{50} for female rats (Sparschu *et al.*, 1971).

Intraperitoneal 2,4,5-T at 50 mg/kg/day for 5 days inhibited *in vivo* development of Ehrlich ascites tumor in mice (Walker *et al.*, 1972).

Teratogenicity. The results of a study by Bionetics Research Laboratories released in 1969 indicated that 2,4,5-T was teratogenic in two stocks of mice 113 mg/kg/day when given during organogenesis (Courtney *et al.*, 1970). Cleft palate, cystic kidneys, intestinal hemorrhage, and fetal mortality occurred in higher percentages of treated than of control mice, although a clear dose-response relation was not evident at low dosages. The 2,4,5-T sample used in this study contained TCDD at 27 ± 8 ppm, and TCDD itself is a teratogen.

To clarify these results, additional sudies were conducted on rats, mice, hamsters, rabbits, sheep, and rhesus monkeys with samples of 2,4,5-T containing varying concentrations of TCDD. No maternal effects, no increases in prenatal mortality, and no fetal malformations resulted when Sprague-Dawley rats were given daily oral doses of a 2,4,5-T preparation containing TCDD at 0.5 ppm on days 5-15 of gestation at up to 24 mg/kg (Emerson *et al.*, 1971). Slight impairment of fetal growth was observed at the highest dosage, i.e., 24 mg/kg/day. In another study by the same group (Johnson, 1971), female rats received were given a 2,4,5-T preparation containing TCDD at 0.5 ppm daily on days 6-15 of gestation at 50 and 100 mg/kg or on days 6-10 at 100 mg/kg. The only effects noted at the lower dosage were one case of intestinal hemorrhage and a slight increase in the frequency of delayed ossification of skull bones. Maternal deaths and reabsorptions occurred at 100 mg/kg/day.

2,4,5-T containing TCDD at 0.5 ppm TCDD was teratogenic in Charles River rats at 80 mg/kg/day, but no fetal or maternal effects were found when the animals received 50 mg/kg/day (Courtney and Moore, 1971). In Wistar rats, 2,4,5-T containing TCDD at less than 0.5 ppm induced fetopathy and increased incidence of skeletal anomalies after daily oral doses of 100-150 mg/kg on days 6-15 of gestation (Khera and McKinley, 1972).

Rats were given 50 mg/kg/day "pure" 2,4,5-T (probably containing TCDD at 0.05 ppm) to which TCDD was added at 0.01, 0.03, 0.06, 0.125, 0.5, or 1.0 μg/kg/day, on days 6-15 of gestation. Cleft palate occurred in some fetuses, mainly the ones that received the 2,4,5-T with TCDD added at 0.5 mg/kg/day (Advisory Committee on 2,4,5-T, 1971).

Teratogenic and embryotoxic effects were seen when NMRI mice were given 2,4,5-T at 50 and 110 mg/kg/day subcutaneously on days 6-14 of gestation (Bage *et al.*, 1973).

Moore (cited by the Advisory Committee on 2,4,5-T, 1971) found no appreciable difference in teratogenic and embryolethal potency between 2,4,5-T as the free acid and its butyl, isooctyl, and butyl ether esters.

Konstantinova (1974) observed embryotoxic effects and maternal toxicity including CNS and hematologic effects after feeding 0.1, 0.42, and 4.2 mg/kg/day of 2,4,5-T butyl ester (0.082, 0.34, 3.4 mg 2,4,5-T equivalent/kg/day) to pregnant albino rats during their entire pregnancy. The no-adverse effect level was reported to be 0.01 mg/kg/day (0.0082 mg 2,4,5-T equivalent/kg/day).

Studies in CD1, C57Bl/6J, and DBA/2J mice strains dosed with 50, 100, 113, 125, or 150 mg/ kg/day of 2,4,5-T containing <1, 0.5, or <0.05 ppm TCDD on days 6-15 of gestation showed some teratogenicity at dosages of 100 mg/kg/day in all three herbicide samples (Courtney and Moore, 1971). Maternal weight was depressed in the C57Bl strain at 100 mg/kg and increased fetal mortality was observed only in CD1 mice at 150 mg/kg.

In another study by the Bionetics Research Laboratories (Advisory Committee on 2,4,5-T, 1971), CD1 mice were given 2,4,5-T from two sources (both containing TCDD at <0.5 ppm) at 100 mg/kg/day subcutaneously on days 6-15 of gestation. Mean fetal weights were slightly reduced, and there was an increased incidence of cleft palate.

The teratogenic effect of technical 2,4,5-T was studied in large numbers of C57Bl/6, C3H-He, BALB/C, and A/JAX inbred strains and CD-1 stock mice (Gaines et al., 1975). The animals were given daily oral doses of 2,4,5-T at 15-120 mg/kg on days 6-14 of gestation. A dosage of 15 mg/kg was teratogenic in A/JAX mice, whereas the other strains and the CD-1 mice showed teratogenicity at 30 mg/kg, the lowest dosage tested. Significant differences in types and frequencies of malformations were observed between the different mice strains.

With the dose-response relationship for the production of cleft palate in mouse fetuses, the ED_{50} single dose of 2,4,5-T (containing TCDD at <0.02 ppm) for NMRI mice was estimated to be 2,000 mg/kg/day (Neubert et al., 1973).

Golden hamsters were treated orally on days 6-10 of gestation with 2,4,5-T at 20-110 mg/kg/day. The 2,4,5-T had seven sources which contained no detectable TCDD or TCDD at 14, 2.9, 0.5 and 0.1 ppm (Collins and Williams, 1971). 2,4,5-T was feticidal and teratogenic in the hamsters, with the incidence and severity of effects increasing with TCDD content. Significantly reduced fetal viability was observed with 2,4,5-T at 20 and 40 mg/kg/day and either no detectable TCDD or 0.5 ppm, whereas significantly increased fetal abnormalities were seen with the same 2,4,5-T samples at 80 and 100 mg/kg/day.

In studies with rabbits (Emerson et al., 1971), no maternal or fetal effects were seen at 2,4,5-T dosages of 40 mg/kg/day.

In a study conducted in Sweden (Advisory Committee on 2,4,5-T, 1971), pregnant rhesus monkeys received 2,4,5-T (containing TCDD at 0.5 ppm) at levels of 5, 10, 20, and 40 mg/kg 3 times a week for 4 weeks between days 20 and 48 of gestation. There were no maternal effects, and all fetuses were apparently normal. Similar effects were seen in rhesus monkeys that received doses of 0.05, 1.0 and 10 mg/kg/day of 2,4,5-T (containing less than 0.05 ppm TCDD) on days 22 through 38 of gestation (Dougherty et al., 1975).

TCDD proved to be a potent fetotoxic agent in various animal species. Fetal weights were slightly decreased and there was a slight increase in intestinal hemorrhage and edema in fetuses from Sprague-Dawley rats that had received TCDD at 0.125

µg/kg/day (Sparschu *et al.*, 1971). The number of fetuses was reduced and fetal death was increased at 0.5 µg/kg/day. No teratogenic effects were seen at 0.03 µg/kg/day.

Fetal kidney malformations were observed when Charles River rats received TCDD subcutaneously at 0.5 µg/kg/day on day 9, day 10, or days 13 and 14 of gestation (Courtney and Moore, 1971).

A low frequency of cleft palate and kidney abnormalities was observed in three mouse lines that received TCDD at 1.0 or 3.0 µg/kg/day (Courtney and Moore, 1971). With a dose-response relationship, Neubert *et al.* (1973) estimated that the ED_{50} causing cleft palate in fetuses was 40 µg/kg/day for NMRI mice. The "just nonteratogenic dose" for days 6-15 of gestation was estimated at 2 µg/kg/day for this mouse strain.

Gastrointestinal hemorrhage was noted in hamster fetuses after administration of TCDD at 0.5 µg/kg/day on days 6-10 of gestation (Advisory Committee on 2,4,5-T, 1971).

IV. CONCLUSIONS AND RECOMMENDATIONS

Although pure 2,4,5-T is moderately toxic, contamination of the herbicide with TCDD, which is very toxic, greatly increases the toxicity. No-adverse effect doses were: for 2,4,5-T, 10 mg/kg/day in dogs and mice, up to 30 mg/kg/day in rats; and for TCDD, 0.01 µg/kg/day in rats. Based on these data ADI's were calculated at 0.1 mg/kg/day for 2,4,5-T and 10^{-4} µg/kg/day for TCDD. The available data on chronic 2,4,5-T and TCDD toxicity and calculations of ADI's are summarized in Tables VI-2 and 3.

There are substantial differences in the reported toxicity of 2,4,5-T, probably because of varying degrees of contamination with TCDD. A number of the subchronic, carcinogenicity, etc., studies should be repeated with 2,4,5-T of very high purity. Apparently, no adequate 2-year chronic-toxicity studies have been conducted with 2,4,5-T, and 2-year feeding studies are needed. The data available are largely from relatively short-term exposure experiments; these data, however, are fairly consistent. An exception is the Russian study in rats which reported toxic effects in mothers and their pups at extremely low maternal doses of 2,4,5-T butyl ester and a no-adverse effect dosage only one-thousandth as high as that found by other investigators. The 2,4,5-T butyl ester used by Konstantinova may have been heavily contaminated with TCDD, but the reason for this large discrepancy is still unexplained and should be resolved.

TABLE VI-7: Summary of Toxicity Data for 2,4,5-T and Esters

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
2,4,5-T					
Human	up to 3 years	(120 manufacturing personnel)	0.01-0.12 mg/kg/day	no toxic effect	Advisory Committee on 2,4,5-T, 1971
Dog	90 days	0-20 mg/kg/day, 4 animals per group	10 mg/kg/day[c]	no toxic effect	Drill and Hiratzka, 1953
Dog			10 mg/kg/day[d]	tolerated	Advisory Committee on 2,4,5-T, 1971
Rat			10 mg/kg/day[d]	tolerated	Advisory Committee on 2,4,5-T, 1971
Mouse	6-15	0-120 mg/kg/day 236-1,585 females per group[e]	15 mg/kg/day	teratogenicity	Gaines *et al.*, 1971
Hamster	6-10	0-100 mg/kg/day 6 females per group[f]	20 mg/kg/day	reduced fetal viability	Collins and Williams, 1971
Rat	6-15	0-24 mg/kg/day 25 females per group[f]	24 mg/kg/day	depressed fetal growth	Emerson *et al.*, 1971
Rat	90 days	0-100 mg/kg/day 20 animals per group[f]	30 mg/kg/day	no toxic effect	Johnson, 1971
2,4,5-T Esters					
Rat	fed through entire pregnancy	0-3.4 mg/kg/day	0.01 mg/kg/day	no toxic effect	Konstantinova, 1974
Rat	90 days	0-186 mg/kg/day	18.6 mg/kg/day	no toxic	Advisory Committee on 2,4,5-T, 1971

Using an uncertainty factor of 100, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{10}{100} = 0.1 \text{ mg/kg/day (ADI)}; \quad 0.1 \times 70^{a} \times 0.1^{b} = 0.7 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Test study from which to calculate suggested no-adverse-effect level.

[d] Unknown TCDD content.

[e] TCDD content estimated at 0.1 ppm.

[f] TCDD content at 0.5 ppm.

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TABLE VI-3. Summary of Toxicity Data for TCDD

Species	Duration of study	Dosage levels & No. of animals per group	Highest no-adverse effect level or lowest-minimal-effect level	Effect measured	Reference
Rat	13 weeks	0, 0.001, 0.01, 0.1, 1.0 µg/kg/day (12 males and 12 females)	0.01 µg/kg/day[c]	no toxic effect	Kociba *et al.*, 1976
Mouse	6 weeks	0, 0.2, 1.0, 0.14, 5.0, 0.71, 25 µg/kg/week (18-24 males)	0.2 µg/kg/week	liver pathology	Vos *et al.*, 1974
Rat	6-13 days	0, 0.03, 0.125, 0.5, 2.0, 8.0 µg/kg/day (10-31 females)	0.03 µg/kg/day	no toxic effect	Sparschu *et al.*, 1971

Using an uncertainty factor of 100, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{0.01}{100} = 0.0001\ \mu g/kg/day\ (ADI),\ 0.0001 \times 70^{a} \times 0.1^{b} = 0.0007\ \mu g/liter$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Calculation of suggested no-adverse-effect drinking water levels.

2,4,5-TP and MCPA

I. INTRODUCTION

2,4,5-TP, or 2,4,5-trichlorophenoxypropionic acid (Silvex), was introduced in 1952 as a selective herbicide for both before and after emergence (USEPA, 1975k; Spencer, 1973; Thomson, 1975; Weed Society of America, 1974). It is available as the amine as well as sodium salts and various esters. The U.S. production is estimated at 3 million pounds per year in 1971 (NAS, 1975) and 3.7 - 4.1 million pounds per year currently (USEPA, 1975k).

MCPA, or 2-methyl-4-chlorophenoxyacetic acid, was introduced in 1945 as a selective, translocated, postemergence herbicide (USEPA, 1975f; Spencer, 1973; Thomson, 1975; Weed Society of America, 1974). It is formulated as amine salts and low-volatility esters. Estimated domestic use of MCPA in 1973 was 3.5-4.5 million pounds (USEPA, 1975f).

2,4,5-TP is produced by reaction of 2,4,5-trichlorophenol with the sodium salt of α-chloropropionic acid (USEPA, 1975k). Commercial 2,4,5-TP contains TCDD at 0.1 ppm or less. It is soluble in water at 180 ppm at 25°C (Weed Science Society of America, 1974).

MCPA is manufactured by chlorination of o-cresol to form 2-methyl-4-chlorophenol, and then coupling with monochloroacetic acid (USEPA, 1975f). Technical MCPA has a typical composition of: MCPA, 94-96%; 2-methyl-6-chlorophenoxyacetic acid, 1.5-3%; a mixture of 2-methyl-4,6-dichlorophenoxyacetic acid, 2-methylphenoxyacetic acid, 2-chlorophenoxyacetic acid, 4-chlorophenoxyacetic acid, and 2,6-dimethyl-4-chlorophenoxyacetic 0.5-1.5%; chloro-o-cresol, 0.5%; and water, 1.0%.

In the FDA Market Basket Survey during 1965-1968, 2,4,5-TP and MCPA were detected at maximal concentrations of less than 0.1 ppm and 0.4 ppm, respectively (Johnson, 1971). During the same period, 2,4,5-TP residues in surface waters from 15 western states ranged between 0.01 and 0.21 ppb. 2,4,5-TP was also detected in the finished water (USEPA, 1976d). The EPA has set an interim standard for 2,4,5-TP in finished water for 0.01 mg/liter (USEPA, 1975l).

II. METABOLISM

The tissue distributions of 2,4,5-TP and its metabolite, 2,4,5-trichlorophenol, were determined in adult sheep and cattle fed for 28 days a diet containing 2,4,5-TP at 300, 1,000 and 2,000 ppm (Clark et al., 1975). Significant residues of both were found only in the liver and kidneys of the treated animals.

The metabolism of MCPA has not been studied extensively, but a metabolite, 2-methyl-4-chlorophenol, was detected in milk of dairy cows and in kidneys of sheep and cattle (USEPA, 1975f). Some unaltered MCPA was detected in the milk, liver, and kidneys of dairy cows.

III. HEALTH ASPECTS

A. Observations in Man. No available data.

B. Observations in Other Species

Acute Effects. The oral LD_{50} of 2,4,5-TP is reported to be 650 mg/kg and 500 mg/kg in rats (Toxic Substances List, 1974; Rowe and Hymas, 1954) and 850 mg/kg in guinea pigs. In rats and rabbits, the oral LD_{50} of the mixed butyl esters and propylene glycol esters ranged between 500 and 1,000 mg/kg (Rowe and Hymas, 1954).

The oral LD_{50} of MCPA is 700-1,410 mg/kg in rats, and 560 mg/kg in mice (Toxic Substances List, 1974; Vershuuren et al., 1975), 550 mg/kg in female guinea pigs, 813 mg/kg in female rabbits, and 940 mg/kg in female chickens. LD_{50} values in the rat and mouse by intraperitoneal administration are 400 and 500 mg/kg, respectively.

Subchronic and Chronic Effects. The propylene glycol butyl ether ester of Silvex (Kuron) was fed to male and female rats in the diet at 10, 30, 100, 300, and 600 mg/kg/day for 90 days (Mullison, 1966; USEPA, 1975k). Mortalities were observed at 600 mg/kg/day, growth decrease at 300 and 600 mg/kg/day, and increased liver weight at 30 mg/kg/day and above. No toxic effect was found in animals receiving 10 mg/kg/day.

In another 90-day study (Mullison, 1966; USEPA, 1975k), male and female rats received the sodium salt of 2,4,5-TP in the diet at 100, 300, 1,000, 3,000, and 10,000 ppm. Growth was decreased at 300 ppm (277 ppm 2,4,5-TP equivalent) and above, and liver weight was increased at 100 ppm (2,4,5-TP equivalent, 92 ppm). Histopathologic examination showed liver and kidney damage at all dietary concentrations, except that the kidneys of females were not affected at 100 ppm.

Beagles were fed Kurosal SL (a formulation containing the potassium salt of 2,4,5-TP at 60%, or the equivalent of 2,4-TP at 53%) of 100, 300, and 1,000 ppm for 89 days (Mullison, 1966; USEPA, 1975k). No adverse effects were noted at 100 ppm or 300 ppm (2,4,5-TP equivalents 53 or 160 ppm), but growth decrease occurred at 1,000 ppm in females.

In a 90-day feeding study of MCPA in rats, growth retardation and increased kidney:body-weight ratios were observed at 400 ppm or more (Verschuuren *et al.*, 1975). The 50-ppm dietary content of MCPA was considered to be the no-adverse effect content for rats by the authors. In another 90-day feeding study in Charles River rats (USEPA, 1975f), significant growth decrease was observed with technical MCPA at 100 ppm, and histopathologic alterations of liver and kidneys were seen in both sexes at 25 ppm or higher. In a later study with the same rat strain, no abnormalities were seen after 90 days in animals fed technical MCPA at 4.0, 8.0 and 16 mg/kg/day (note that 4.0 mg/kg/day is approximately equivalent to a dietary content of 25 ppm).

Some dogs that received daily oral doses of technical MCPA over a 13-week period died, and all showed severe weight loss at 50 mg/kg/day, whereas more moderate weight losses but no mortalities occurred at 25 mg/kg/day (USEPA, 1975f). In another 13-week study, decreased testicular weight and histopathologic changes of the testes and prostate were seen in dogs fed technical MCPA at 640 ppm.

Male and female rats were fed Kurosal SL at 10, 30, 100 and 300 ppm for 2 years (Mullison, 1966; USEPA, 1975k). Increased kidney weight was seen in males that received 300 ppm, but there were no-adverse effects at 10, 30, and 100 ppm. The no-adverse effect concentration was considered to be 100 ppm (2,4,5-TP equivalent, 53 ppm) (Mullison, 1966). The same formulation was fed to beagles 56, 190 and 560 ppm for 2 years (Mullison, 1966; USEPA, 1975k). Dogs fed 560 ppm showed severe liver pathology after 1 year. At 190 ppm, liver pathology was seen in females sacrificed after 1 year, but not in animals sacrificed at 2 years; in males, no liver pathology was seen at 1 year, but it was present at 2 years. The no-adverse effect content thus was 56 ppm (2,4,5-TP equivalent, 30 ppm) for males and 190 ppm (2,4,5-TP equivalent, 101 ppm) for females (Mullison, 1966). Another report cited 5 mg/kg/day as the no-adverse-effect dosage for 2,4,5-TP in rats and dogs in 2-year feeding studies (Johnson, 1971).

When technical MCPA was fed to rats for 7 months, some deaths occurred at 2,500 ppm, and a significant reduction in weight occurred at 1,000 and 2,500 ppm (USEPA, 1975f). No apparent toxic effects were noted in animals that received 100 and 400 ppm (66.8 mg/kg/day).

Mutagenicity. 2,4,5-TP did not cause point mutations in histidine-requiring mutants of *Salmonella typhimurium* or bacteriophage T (Anderson *et al.*, 1972).

MCPA has been found to be a weak mutagen in *Drosophila melanogaster* (Vogel and Chandler, 1974).

Carcinogenicity. Young male and female mice of the (C57BL/6 x C3H/Anf)F and the (C57BL/6 x AKR)F strains received 2,4,5-TP orally at 46.4 mg/kg/day on days 7-28 and thereafter were placed on a diet containing 2,4,5-TP at 121 ppm for approximately 18 months (Innes *et al.*, 1969). There was no increase in the incidence of tumors above control values for either strain.

Teratogenicity. Courtney (1975) examined the effect of 2,4,5-TP containing TCDD at less than 0.1 ppm on pregnant CD-1 strain mice and their offspring. Animals received daily 2,4,5-TP at 398 mg/kg/day orally or subcutaneously on days 12-15 of gestation. Controls had no cleft palates, whereas the herbicide produced 3% (oral) or 7% (subcutaneous) cleft palates in the fetuses. There was also a significant increase in maternal liver:body-weight ratios in the treated mice.

In a study conducted by Dow (USEPA, 1975k), Sprague-Dawley rats were given 2,4,5-TP at 25, 50, 75, 100, or 175 mg/kg/day on days 6-15 of gestation or 50, 75, or 100 mg/kg/day from day 6 of gestation through lactation. A few maternal deaths occurred at 100 mg/kg/day; the dosage of 75 mg/kg/day produced alopecia and vaginal bleeding. Minor alopecia was seen at 50 mg/kg/day. Terata were seen at 50 mg/kg/day, but were minor and related to incomplete ossification of the skull. Mean pup weights were significantly decreased at 50 mg/kg/day and above. The dosage with no adverse fetotoxic effects was considered to be 25 mg/kg/day.

The teratogenic potential of the propylene glycol butyl ether ester of 2,4,5-TP (containing TCDD at less than 0.05 ppm) was tested in rats (USEPA, 1975k). Significant increases in minor skeletal abnormalities were observed at 50 mg/kg/day; at 35 mg/kg/day of 2,4,5-TP. No overt teratogenicity was seen.

Female Wistar rats were fed MCPA (ethyl ester) at 1, 40, 500, 1,000, and 2,000 ppm in the diet on days 8-15 of gestation (USEPA, 1975f). Fetal mortalities occurred at 2,000 ppm, and a dose-dependent decrease in fetal weight and an increase in fetal abnormalities occurred at 1,000 ppm.

Female mice were fed technical MCPA at 5, 25, and 100 mg/kg/day on days 6-15 of gestation (USEPA, 1975f). Litter and mean pup weights were reduced at 100 mg/kg/day, but no major malformations were observed.

Pregnant Wistar rats were fed with MCPEE (the ethyl ester of MCPA) at 30, 500, 1,000, and 2,000 ppm (about 2.7, 30, 60, and 100 mg/kg/day) on days 8-15 of gestation (Yasuda and Maeda, 1972). No adverse effects were noted at 30 and 500 ppm, but 1,000 and 2,000 ppm caused a decrease in fetal weight and increased teratogenesis. The highest dosage also caused a reduction in maternal weight.

IV. CONCLUSIONS AND RECOMMENDATIONS

In two-year feeding studies the no-adverse-effect doses for 2,4,5-TP are at up to 5 mg/kg/day and 6.8 mg/kg/day in dogs and rats respectively. In 90-day feeding studies no-adverse-effect doses were reported at up to 10 mg/kg/day for MCPA in rats, but histopathologic changes in livers and kidneys were reported once at 1.25 mg/kg/day. Based on these data ADI's were calculated at 0.00075 mg/kg/day for 2,4,5-TP and 0.00125 mg/kg/day for MCPA.

The available chronic toxicity data and calculations of ADI's on 2,4,5-TP and MCPA are summarized in Tables VI-4 and 5.

There is considerable variation in the no-adverse-effect and minimal-toxic-effect dosages found in the various subchronic-toxicity experiments with MCPA. The reasons for these differences are not apparent, and further work is needed to resolve them. There have been no 2-year chronic-toxicity tests with MCPA, and such studies should be undertaken. Moreover, very little is known about the reproductive, mutagenic, and carcinogenic properties of MCPA. Additional research is needed, particularly in view of the reported weak mutagenic activity of MCPA.

Further studies on 2,4,5-TP are also needed to determine whether the observed toxicity and teratogenicity are intrinsic in the herbicide or are due to contamination with TCDD.

There appears to be a complete lack of data on human toxicity related to either herbicide.

TABLE VI-4: Summary of Chronic and Subchronic Toxicity Data for 2,4,5-TP (Silvex)

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Dog	2 years	0-300 ppm in diet	30 ppm (0.75 mg/kg/day)[c,d]	no toxic effect measured in males	Mullison, 1966; EPA, 1975b
Rat	2 years	0-160 ppm in diet 50 animals per group	53 ppm (2.6 mg/kg/day)[d]	no toxic effect	Mullison, 1966; EPA, 1975b
Dog	89 days	0-534 ppm in diet	160 ppm (4.0 mg/kg/day)[d]	no toxic effect	Mullison, 1966; EPA, 1975b
Rat	90 days	0-9,200 ppm in diet	92 ppm (4.6 mg/kg/day)[d]	increased liver weight, liver and kidney pathology	Mullison, 1966; EPA, 1975b
Rat	90 days		9 mg/kg/day	no toxic effect	Johnson, 1971
Dog	2 years		5 mg/kg/day	no toxic effect	Johnson, 1971
Rat	90 days	0-408 mg/kg/day	6.8 mg/kg/day	no toxic effect	Mullison, 1966; EPA, 1975b

Using an uncertainty factor of 1000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{0.75}{1000} = 0.00075 \text{ mg/kg/day (ADI)}; \quad 0.00075 \times 70^a \times 0.1^b = .00525 \text{ mg/liter}$$

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[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Calculation of suggested no-adverse-effect drinking water levels.

[d] Assume weight of rat = 0.4 kg and dog = 10 kg; assume daily food consumption of rat = 0.02 kg and of dog = 0.25 kg.

TABLE VI-5: Summary of Chronic and Subchronic Toxicity Data for MCPA

Species	**Duration of Study**	**Dosage Levels & No. of Animals Per Group**	**Highest No-Adverse-Effect Level or Lowest-Minimal Effect Level**	**Effect Measured**	**Reference**
Rat	90 days	0-100 ppm in diet	25 ppm (1.25 mg/kg/day)[c,d]	liver and kidney pathology	EPA, 1975f
Rat	90 days	0-200 ppm in diet	50 ppm (2.5 mg/kg/day)[d]	no toxic effect	Verschuuren, *et al.*, 1975
Dog	13 weeks	640 ppm	640 ppm (16 mg/kg/day)[d]	testicular damage	EPA, 1975f
Rat	90 days	0-16 mg/kg/day	16 mg/kg/day	no toxic	EPA, 1975f
Rat	7 months	0-2,500 ppm in diet	400 ppm (20 mg/kg/day)[d]	no toxic effect	EPA, 1975f
Dog	13 weeks	0-75 mg/kg/day orally, 4 animals per group	25 mg/kg/day	weight loss	EPA, 1975f

Using an uncertainty factor of 1000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{1.25}{1000} = 0.00125 \text{ mg/kg/day (ADI)}, \quad 0.00125 \times 70^{a} \times 0.1^{b} = 0.009 \text{ mg/liter}$$

[a] Assume average weight of human adu[illegible] 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Calculation of suggested no-adverse-effect drinking water levels.

[d] Assume weight of rat = 0.4 kg and dog = 10 kg; assume daily food consumption of rat = 0.02 kg and of dog = 0.25 kg.

2. BENZOICS

AMIBEN

I. INTRODUCTION

Amiben, or 3-amino-2,5-dichlorobenzoic acid (Chloramben) is used as a selective preemergence herbicide (Spencer, 1973; Thomson, 1975). It was introduced in 1958. Annual production of amiben in the United States is estimated at 20 million pounds (NAS, 1975). The herbicide is formulated as the ammonium salt and the methyl ester.

Amiben is synthesized by chlorination of benzoic acid, followed by interaction and reduction (Spencer, 1973). Water solubility of Amiben is 700 ppm at 25°C (Weed Science Society of America, 1974).

II. METABOLISM. No available data.

III. HEALTH ASPECTS

A. Observations in Man. No available data.

B. Observations in Other Species

Acute Effects. The oral LD_{50} of Amiben in rats is 3,500-5,620 mg/kg in rats, and the dermal LD_{50} in rabbits is 3,136 mg/kg (Ben-Dyke *et al.*, 1970).

Chronic Effects. Amiben was fed to Charles River rats over a period of 2 years at dietary concentrations of 100, 1,000, and 10,000 ppm (Hazelton *et al.*, 1964). No adverse effects were found on growth, food consumption, mortality, tumor incidence, hematologic characteristics, or tissue morphology.

Male and female beagles were fed Amiben at concentrations of 100, 1,000, and 10,000 ppm for an unspecified period; there were no dose-related effects on mortality, growth, hematologic values, biochemical characteristics, or tissue histopathology (Hazelton *et al.*, 1964).

Mutagenicity. No mutagenic activity for Amiben was noted in bacteria (Anderson *et al.*, 1972).

Carcinogenicity. No available data other than the Hazelton study (Hazelton *et al.*, 1964).

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

The available data on Amiben are very sparse. Much additional information is needed regarding its chronic toxicity, teratogenicity, and carcinogenicity before approval limits can be confidently set. It is possible that many pertinent studies have been conducted by the manufacturer and could be made available for evaluation.

No-adverse-effect doses for Amiben were at 250 mg/kg/day and 500 mg/kg/day in dogs and rats, respectively, in feeding studies. Based on these data an ADI was calculated at 0.25 mg/kg/day.

The limited data available and calculations of ADI are summarized in Table VI-6.

TABLE VI-6; Summary of Chronic Toxicity Data for Amiben

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Dog	presumably 2 years	0-10,000 ppm, 8 animals per group	10,000 ppm (250 mg/kg/day)[c,d]	no toxic effect	Hazelton *et al.*, 1964
Rat	2 years	0-10,000 ppm females, 70 animals per group	10,000 (500 mg/kg/day)[d]	no toxic effect	Hazelton *et al.*, 1964

Using an uncertainty factor of 1000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{250}{1000} = 0.25 \text{ mg/kg/day (ADI)}, \quad 0.25 \times 70^{a} \times 0.1^{b} = 1.75 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Calculation of suggested no-adverse-effect drinking water levels.

[d] Assume weight of rat = 0.4 kg and dog = 10 kg; assume daily food consumption of rat = 0.02 kg and of dog = 0.25 kg.

DICAMBA

I. INTRODUCTION

Dicamba, or 2-methoxy-3,6-dichlorobenzoic acid, is used as a preemergence herbicide for control of annual broadleaf and grassy weeds (USEPA, 1975c). Annual production of Dicamba in the United States has been estimated at 6 million pounds (NAS, 1975), but total domestic use was believed to be 1.2 million pounds in 1974 (USEPA, 1975c).

Dicamba is synthesized from hexachlorobenzene via 1,2,4-trichlorobenzene to 2,5-dichlorophenol to 2-hydroxy-3,6-dichlorobenzoic acid (USEPA, 1975c). The composition of technical grade dicamba is 2-methoxy-3,6-dichlorobenzoic acid 80-93%; 2-methoxy-3,5-dichlorobenzoic acid 7-20%; and 3,6-dichlorosalicylic acid 0.5-5%. Dicamba formulations usually involve the alkali metal or alkylamine salts, and it is often formulated in combination with other herbicides (MCPA, 2,4-D etc.). Dicamba is soluble at 4,500 ppm in water. It is chemically resistant to breakdown, and it persists in soils for 7-10 months. It is not strongly adsorbed onto soils, and it is readily leached by runoff waters. Volatilization of Dicamba is low. It is resistant to oxidation and reasonably resistant to hydrolysis, but is degraded by ultraviolet light to 3,6-dichlorosalicylic acid and unidentified compounds.

In field tests, runoff-water residues of Dicamba from field plots were found to be 1.6-9.8 ppm after 24 h (Trichell *et al.*, 1968). Rapid loss occurs, however, in water.

No residues of Dicamba have been found in foods in the FDA "total diet" samples (Manske and Johnson, 1975).

Golavan (1970) reported that the smell and taste threshold for Dicamba in water was about 200 ppm. On the basis of various toxicity tests, the U.S.S.R. recommended maximal permissible concentration of Dicamba in water is 15 ppm.

II. METABOLISM

When ^{14}Carboxyl-labeled Dicamba was administered orally to male and female Charles River CD rats, 0.8-1.1% of the radioactive dose was recovered in the feces, 92.88-99.1% in the urine, 0.0-0.3% in the gastrointestinal tract, and 0.5-2.1% in the tissues after 72 h (Tye and Engel, 1967). In a second experiment, groups of Charles River CD rats were fed ^{14}C-labeled Dicamba in the diet at 10, 100, 1,000, 10,000, or 20,000 ppm over a 24-day period. Fecal excretion averaged 1.8-4.4%, whereas excretion in the urine was 97.4% of the administered radioactive dose. Approximately two-thirds of the urinary radioactivity was in unchanged Dicamba, and 12-20% was in the glucuronide conjugate of Dicamba. No evidence of the sulfate conjugate or of 3,6-dichlorosalicylic acid was found.

Urine contained 73% of the Dicamba fed to a Holstein cow after 7 days (St. John and Lisk, 1969). Unchanged Dicamba and 3,6-dichlorosalicylic acid have been identified in the urine of a heifer fed Dicamba (USEPA, 1975c).

In studies conducted in a model ecosystem (Yu *et al.*, 1975), Dicamba was shown to persist in water in conjugated and in anionic forms. It was slowly transformed to 5-hydroxydicamba in water (about 10% after 32 days) and was slowly decarboxylated. No evidence of food-chain magnification of Dicamba was obtained.

III. HEALTH ASPECTS

A. Observations in Man. No available data.

B. Observations in Other Species

Acute Effects. Reported acute oral LD_{50} values for technical Dicamba in rats range between 757 and 2,900 mg/kg (Edson and Sanderson, 1965; USEPA, 1975c; Golavan, 1970). Salts of Dicamba showed similar acute toxicities to rats (oral LD_{50}, 1,000-2,000 mg/kg). The acute LD_{50} of technical Dicamba in male rats on intraperitoneal injection, however, was only 80 mg/kg. Male rats were more susceptible to orally administered technical dicamba (LD_{50}, 757 mg/kg) than were females (LD_{50}, 1,414 mg/kg). Inasmuch as pure Dicamba had an oral LD_{50} in female rats of more than 2,560 mg/kg contaminants of the technical herbicide may be more toxic than the herbicide. The oral LD_{50} in rats of 3,6-dichlorosalicylic acid, the major Dicamba decomposition product, was 1,440 mg/kg.

The oral LD_{50} of technical Dicamba in mice was 1,189 mg/kg whereas oral LD_{50}'s for various Dicamba salts in mice, rabbits, guinea pigs, and chickens were over 4,640, 566, 566, and 673 mg/kg, respectively (Edson and Sanderson, 1965; USEPA, 1975c). Signs of acute Dicamba poisoning in animals include muscle spasms, bradycardia, and inhibited voluntary and involuntary reflexes. Death occurs within 3 days.

Subchronic and Chronic Effects. Concentrations of Banvel D (Dicamba, 41.3% 14.6% dimethylamine, 14.6%; and water, 44.1%) ranging from 658 to 23,500 ppm were fed to weanling Charles River CD strain rats for 3 weeks, with no significant effect (USEPA, 1975c). In another study, male and female Sprague-Dawley rats were fed diets Banvel D at 100, 500, 800, and 1,000 ppm for 13 weeks. Hypersensitivity was noted in the rats fed 1,000 ppm (equivalent to Dicamba at 413 ppm). Moderate necrosis and vacuolization of the liver were seen in rats fed 1,000 (equivalent to Dicamba at 413 ppm), slight liver pathology in rats fed 800 ppm (330 ppm Dicamba), and no adverse effect in rats fed 500 ppm (206 ppm Dicamba) (USEPA, 1975c). In a third study, Wistar rats were fed diets containing Dicamba at 31.6, 100, 316, 1,000, or 3,162 ppm for a 15-week period (Edson and Sanderson, 1965). Liver:body-weight ratios were increased in animals receiving Dicamba at 1,000 and 3,162 ppm, and the no-adverse-effect dosage was estimated to be 316 ppm (19.3 mg/kg/day).

Purebred beagles of both sexes were fed diets containing Dicamba at 100 or 250 ppm for 90 days (USEPA, 1975c). The only adverse finding was a slight yellowish cast to the liver in 2 of the 4 dogs on the 100-ppm diet and 1 of the 4 dogs on the 250-ppm diet.

Dicamba was administered orally to an unspecified strain of rat for 5 months at 0.075, 0.75, or 7.5 mg/kg/day (Rudzina and Golovan, 1972). Unspecified toxicity was seen at 7.5 mg/kg/day. In another study, Sprague-Dawley rats of both sexes were fed diets containing technical Dicamba (90% Dicamba) at 5, 50, 100, 250, or 500 ppm for 2 years (USEPA, 1975c; Velsicol Chemical Corp., 1967). These diets did not produce differences in survival, body weight, food consumption, organ weights, hematologic values, or histopathologic findings.

Purebred beagles of both sexes were fed diets containing technical Dicamba (90% Dicamba) at 5, 25, or 50 ppm for 2 years (USEPA, 1975c; Velsicol Chemical Corp., 1967). No major differences were seen between control and treated groups in to mortality, growth, food consumption, organ weights, hematologic values, or histopathology.

Mutagenicity. No mutations were noted in the *Salmonella*/microsome test with Dicamba (USEPA, 1975c), and no mutagenic effects were noted in other systems (Anderson *et al*., 1972).

Carcinogenicity. No evidence of tumor induction by Dicamba has been reported.

Reproduction. In a three-generation Charles River CD rat reproduction study, no significant effects were observed in animals receiving diets containing Banvel D at up to 500 ppm (206 ppm Dicamba) (USEPA, 1975c; Velsicol Chemical Corp., 1967). A similar study in Sprague-Dawley rats showed no effect at a dietary Dicamba concentration of 500 ppm.

Teratogenicity. A 50% reduction in hatchability was noted in chicken eggs into which Dicamba was injected at 200 ppm (USEPA, 1975c).

IV. CONCLUSIONS AND RECOMMENDATIONS

The acute toxicity of Dicamba is relatively low. Dicamba produced no-adverse effect when fed to rats at up to 19.3 mg/kg/day and 25 mg/kg/day in subchronic and chronic studies. The no-adverse effect dose in dogs was 1.25 mg/kg/day in a 2 year feeding study. Based on these data an ADI was calculated at 0.00125 mg/kg/day. The available data on subchronic and chronic toxicity and calculations of ADI are summarized in Table VI-7.

A detection limit of 1 ppb for Dicamba by electron capture gas chromatography has been reported (Morris and Montgomery, 1975).

Additional studies are needed to clarify the finding of toxicity in subchronic experiments on various strains of rats in the absence of adverse effects in rats fed higher Dicamba concentrations over a 2-year period. Because toxicity was not observed in chronic toxicity studies in dogs, additional chronic studies should be conducted at higher dosages to establish a minimal-toxic-effect dosage.

TABLE VI-7: Summary of Chronic and Subchronic Toxicity Data for Dicamba

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Rat	6 months	0-75 mg/kg/day	0.75 mg/kg/day	no toxic effect	Rudzina and Golovan, 1971
Dog	2 years	0-50 ppm in diet 6 animals per group	50 ppm (1.25 mg/kg/day)[c,d]	no toxic effect	EPA, 1975c; Pond *et al.*, 1975
Rat	13 weeks	0-413 ppm in diet, 30 animals per group	206 ppm (10.3 mg/kg/day)[d]	no toxic effect	EPA, 1975c; Pond *et al.*, 1975
Rat	15 weeks	0-3, 162 ppm in diet, 30 males per group	316 ppm (15.8 mg/kg/day)[d]	no toxic effect	Edson and Sanderson, 1965

Using an uncertainty factor of 1000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{1.25}{1000} = 0.00125 \text{ mg/kg/day (ADI)}, \quad 0.00125 \times 70^{a} \times 0.1^{b} = 0.009 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Calculation of suggested no-adverse-effect drinking water levels.

[d] Assume weight of rat = 0.4 kg and dog = 10 kg; assume daily food consumption of rat = 0.02 kg and of dog = 0.25 kg.

3. AMIDES

ALACHLOR, BUTACHLOR, AND PROPACHLOR

I. Introduction

Among the several herbicidal compounds based on *N*-substituted acetanilide are the compounds Alachlor, or 2-chloro-2',6'-diethyl-*N*-(methoxymethyl)-acetanilide; Butachlor, or 2-chloro-2',6'-diethyl-*N*-(butoxymethyl)-acetanilide; and Propachlor, or 2-chloro-*N*-isopropyl-*N*-acetanilide. These are used as preemergence herbicides and, under the trade names of Lasso (Alachlor), Machete (Butachlor), and Ramrod (Propachlor), are achieving a strong position in that market. Alachlor and Propachlor have major use in corn and soybean producton, and Butachlor is used primarily in rice production. 14.8 million pounds of Alachlor and 23.7 million pounds of Propachlor were used by farmers in 1971 in the U.S. (NAS, 1975). It was estimated that 20 million pounds of Alachlor and 23 million pounds of Propachlor were produced in the U.S. in 1961 (NAS, 1975).

These compounds are slightly soluble in water: Alachlor at 242 ppm at 25°C, Butachlor at 23 ppm at 24°C, and Propachlor at 580 ppm at 20°C (Weed Science of America, 1974). They are rated as having good resistance to photodecomposition with no ultraviolet absorption above 280 nm, which lies below the minimal wavelength of solar radiation received at the earth's surface.

It has been reported that Alachlor and Propapachlor are labile in an aquatic environment and there was no evidence to indicate that the metabolites or degradation products were accumulated in the biota (Yu, *et al.*, 1975).

Alachlor and Butachlor have been found in the finished water of New Orleans area at 2.9 µg/l for Alachlor and 1.21 µg/l for Butachlor (USEPA, 1975n).

II. METABOLISM

Rapid excretion of ^{14}Carbonyl-Propachlor administered to rats was observed, with 54-64% of the carbon-14 appearing in the urine within 24 h (Lamboureux *et al.*, 1975). Three major urinary products were found, one of which was identified as the mercapturic acid resulting from glutathione conjugation with Propachlor. The mercapturic acid excreted within 24 h accounted for 20% of the dose. The other major metabolites were not identified, but were not related to glutathione conjugation.

III. Health Aspects

A. Observations in Man. No available data.

B. Observations in Other Species

Acute Effects. These products are generally well tolerated. Alachlor, as the emulsifiable concentrate, has a rat oral LD_{50} of 1,800 mg/kg; Butachlor, 3,300 mg/kg; and Propachlor, 710 mg/kg (Weed Science Society of America, 1974).

Subchronic and Chronic Effects. Subchronic toxicities in rats are reported to be over 2,000 ppm in the diet, at least over 2,000 ppm, and over 133.3 mg/kg/day for Alachlor, Butachlor, and Propachlor, respectively. With Alachlor, the growth patterns of rats and dogs were normal at 20, 200, and 2,000 ppm for a 90-day period; some growth decrease was observed at a higher rate of feeding. Butachlor administration at those concentrations produced similar results, except for slight growth decrease at 2,000 ppm in rats. Increased liver weight was observed in female rats fed Butachlor at 200 and 2,000 ppm. Propachlor was tolerated, without adverse clinical effects or gross or microscopic pathology, by rats and dogs fed at 1.3 - 133.3 mg/kg/day for 90 days (Herbicide Handbook, 1974). However, Propachlor has been reported to cause dystrophic changes in the liver and kidneys of rats, mice, and rabbits when administered at 100 - 1,800 mg/kg. The effects depended on dosage and were accompanied by decreased activities of various enzyme markers of cellular organelles (Strateva et al., 1974). No data on long-term toxicity of these herbicides are available. Nor are data on reproduction, mutagenicity, teratogenicity, or carcinogenicity.

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

Although the toxicity data on this group of compounds are meager, they appear to be fairly well tolerated by mammals. Propachlor, the most toxic of the group, has received somewhat more attention.

Tolerances of 0.2 - 0.75 ppm for peanut, soybean, and other legume forages has been established for Alachlor; it is also tolerated at 0.05 ppm in fresh corn (kernels) and peanuts. A 0.02-ppm (negligible residue) tolerance for Alachlor applies to meat, eggs, and milk.

The maximal tolerated dosage of Propachlor without adverse effect is reported as 133.3 mg/kg/day in both rats and dogs. Other workers reported slight organ pathology in rats, mice, and rabbits at 100 mg/kg/day or higher; this agrees approximately with the former data. Both Alachlor and Butachlor are apparently tolerated by rats at up to 100 mg/kg/day in the diet, except for increased liver weight in female rats fed Butachlor.

The existing toxicity data for these compounds are largely those produced by the manufacturer for registration purposes. Based on the above available data ADI's were calculated at 0.1, 0.1, and 0.01 mg/kg/day for Alachlor, Propachlor, and Butachlor, respectively. The available data on subchronic toxicity and calculation of ADI's are summarized in Table VI-8.

Apparently, no long-term toxicity studies have been completed that would contribute information on reproductive effects or carcinogenic potential of these acetanilides or their degradation products, which include aniline derivatives. These studies are needed.

TABLE VI-8: Summary of Toxicity Data for Alachlor, Butachlor and Propachlor

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
PROPACHLOR					
Rat	90 days	1.3 to 133.3 mg/kg/day	133.3 mg/kg/day	no mortality, No organ path	Weed Science Society of America, 1974
Dog	90 days	1.3 to 133.3 mg/kg/day (number not available)	133.3 mg/kg/day	no mortality, No organ path	WSSA, 1974
Rat		100 to 1800 mg/kg/day (number not available	100 mg/kg/day[c,d]	distrophic liver and kidney	Strateva *et al* 1974
ALACHLOR					
Rat, Dog	90 days	20, 200, 2000 ppm in diet (number not available)	2000 ppm (100 mg/kg/day)[c,d]	no-adverse effect	WSSA, 1974
BUTACHLOR					
Rat Dog	90 days	20, 200, 2000 ppm in diet (number not available)	2000 ppm (dog) 200 ppm (rat) (10 mg/kg/day)[c,d]	no-adverse effect increased liver weight	WSSA, 1974

Using an uncertainty factor of 1000, suggested no-adverse-effect levels in drinking water are calculated as follows:

Alachlor: $\frac{100}{1000}$ = 0.1 mg/kg/day (ADI), $0.1 \times 70^{a} \times 0.1^{b}$ = 0.7 mg/liter

Butachlor: $\frac{10}{1000}$ = 0.01 mg/kg/day (ADI), $0.01 \times 70^{a} \times 0.1^{b}$ = 0.07 mg/liter

Propachlor: $\frac{100}{1000}$ = 0.1 mg/kg/day (ADI), $0.1 \times 70^{a} \times 0.1^{b}$ = 0.7 mg/liter

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[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Calculation of suggested no-adverse-effect drinking water levels.

[d] Assume weight of rat = 0.4 and of dog = 10 kg; assume daily food consumption of rat = 0.02 kg and of dog = 0.25 kg.

PROPANIL

I. INTRODUCTION

Propanil, or 3',4'-dichloropropionanilide, is a preemergence herbicide registered for use in rice to control grasses, sedges, and some broadleaf weeds. Use in the United States has been primarily in the rice-growing regions of Texas, Arkansas, Louisiana, and Mississippi; little has been used in California. Domestic consumption was around 8-9 million pounds in 1973 (USEPA, 1975o). Propanil is produced by reaction of 3,4-dichloroaniline with propionic acid at high temperature (Melnikov, 1971). It is soluble in water at 500 ppm (Weed Science Society of America, 1974).

II. METABOLISM

Propanil is hydrolysed by the action of hepatic acylamidase, forming 3,4-dichloroaniline and propionic acid (Williams et al, 1966). The enzyme has been shown to be present in the liver of rats, mice, rabbits, and dogs. Other conversions are brought abo[illegible] either on propanil itself or on dichloroaniline, giving r[illegible]o at least six metabolites in urine; these metabolites con[illegible]itute about 95% of the urinary products (Yih et al., 1970). Little radioactivity from labeled propanil appeared in tissues in short duration experiments with rats, mice, and dogs; this indicates that the propensity for accumulation of propanil or its metabolites in tissues is slight (USEPA, 1975o).

Methemoglobin formation occurs in mice treated with propanil. After a large dose (400 mg/kg), cyanosis becomes apparent, although no other symptoms of toxicity occur (Chow et al., 1975). The methemoglobin formation is due to the dichloroaniline liberated by acylamidase.

III. HEALTH ASPECTS

A. Observations in Man. No available data.

B. Observations in Other Species

Acute Effects. Ambrose et al. found oral LD$_{50}$ values of 1,384 mg/kg for rats and 1,217 mg/kg for dogs (Ambrose, 1972); these values were observed with technical propanil. Proprietary data summarized by Midwest Research Institute indicated that rats of both sexes tolerated repeated doses of up to 60 mg/kg for [illegible] days and dietary administration at up to 200 ppm for 90 days without any effects (USEPA, 1975o). Ambrose et al. (1972) fed technical propanil to Wistar rats for 90 days at 100, 333, 1,000, 3,300, 10,000, and 50,050 ppm in the diet. Mortality was 100% at

50,000 ppm; body weight was depressed at 3,300 and 10,000 ppm, and there was a significant increase in polychromatophilia and other evidence of hemolytic anemia. Dogs were unaffected by propanil fed at 2,000 ppm for 4 weeks, but 10,000 and 50,000 ppm caused decreased food consumption and weight loss (Ambrose *et al.*, 1972).

Chronic Effects. Two-year feeding trials with rats were conducted by Ambrose *et al.* (1972) with dietary concentrations of 100, 400, and 1,600 ppm. No effects were observed, except 1,600 ppm (of both sexes). Males experienced increased mortality at 20 months, females had significantly reduced hemoglobin concentrations, and both sexes experienced body-weight decrease and increased spleen:body weight ratios. No histopathologic alternations were found.

Dog feeding studies with propanil at 100, 600, and 3,000 ppm (4,000 ppm after week 5) were carried out for 2 years (Ambrose *et al.*, 1972). No mortalities occurred, nor were any clinical, gross pathologic or histopathologic changes found; the only effect observed was decreased feed efficiency at 4,000 ppm.

Mutagenicity. Propanil and its degradation products, dichloroaniline and 3,3',4,4'-tetrachloroazobenzene (TCAB), were tested for back mutations of *Aspergillus nidulans* (Prasad 1970). Propanil did not increase the frequency of reversion when added to fungal conidia in concentrations of 5 - 200 µg/ml of medium. However, 3,4-dichloroaniline and TCAB both caused several-fold increases in reversion rates. Propanil has also been found negative in tests of induction of point mutations in three microbial systems (Anderson *et al.*, 1972).

Carcinogenicity. No available data.

Reproduction. A three-generation reproduction study in Wistar rats was reported by Ambrose *et al.* (1972). Dietary concentrations of 100, 300, and 1,000 ppm were fed to groups of females for 11 weeks before they mated with males receiving similar diets. No changes in reproductive performance were found in any generation (to the F3) at any dosage, nor were fetal abnormalities observed in fetuses born dead or alive or in rats necropsied with fetuses *in utero*.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

Propanil is well tolerated by experimental animals on a chronic basis, and there is little or no indication of mutagenic or oncogenic properties of the compound. The highest no-adverse-effect concentration of propanil--based on reproduction in the rat and acute, subchronic, and chronic studies in rats and dogs--is 400 ppm in the diet. Based on these data an ADI was calculated at 0.02 mg/kg/day. The available data on chronic toxicity and calculations of ADI are summarized in Table VI-9.

TABLE VI-9. Summary of Chronic Data for Propanil

Species	Duration of study	Dosage levels and No. of animals per group	Highest no-adverse-effect level or lowest-minimal-effect level	Effect Measured	Reference
Rat	2 yrs	100, 400, 1,600 ppm (50 per group, equal F, M)	400 ppm (20 mg/kg/day)^{c,d}	No adverse effect	Ambrose et al., 1972
Dog	2 yrs	100, 600, 4,000 ppm (4 per group, equal F, M)	4,000 ppm (100 mg/kg/day)^{d}	No adverse effect	Ambrose et al., 1972
Rat	3-generation	100, 300, 1,000 ppm (20 F per group at start)	1,000 ppm (50 mg/kg/day)^{d}	No reproductive effects	Ambrose et al., 1972

Using an uncertainty factor of 1,000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{20}{1000} = 0.02 \text{ mg/kg/day (ADI)}, \; 0.02 \times 70^{a} \times 0.1^{b} = 0.14 \text{ mg/liter.}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Test study from which to calculate suggested no-adverse-effect level.

[d] Assume weight of rat = 0.4 kg and of dog = 10 kg; average daily food consumption of rat = 0.02 kg and of dog 0.25 kg.

8. TRIAZINES

ATRAZINE, SIMAZINE, PROPAZINE, CYANAZINE

I. INTRODUCTION

These four herbicides are all derivatives of cyanuric chlorides and are closely related in environmental properties. Atrazine is 2-chloro-4-ethylamino-6-isopropylamino-*s*-triazine; Simazine is 2-chloro-4,6-diethylamino-*s*-triazine; Propazine is 2-chloro-4,6-diisopropylamino-*s*-triazine; and Cyanazine is 2-chloro-4-(1-cyano-1-methylethylamino)-6-ethylamino-*s*-triazine.

These herbicides are used largely in preemergence applications for corn, sorghum, and sugar cane, with minor use on pineapple, macadamia orchards, and turf grasses especially (Atrazine). Simazine is also used in citrus, deciduous fruits, pineapple, turf grasses, ornamentals, and nursery plantings (WSSA, 1974).

United States production is estimated as: Atrazine, 90 million pounds; Simazine, 5 million pounds; Propazine, 4 million pounds; and Cyanazine, 3 million pounds (NAS, 1975). Atrazine is the pesticide most heavily used in the United States.

The solubilities of the triazine herbicides in water at 25°C are: Atrazine, 70 ppm; Simazine, 5.0 ppm, Propazine, 8.6 ppm; and Cyanazine, 171 ppm (WSSA, 1974).

Atrazine was found in the New Orleans water supply at 4.7, 5.0, and 5.1 ppb, and diethylatrazine at 0.27-0.51 ppb (USEPA, 1974a). Atrazine was monitored in Iowa surface and ground water in Iowa by Richard *et al.* (1975). In the Skunk River residues declined from 12.0 ppb on June 9, 1974 to 0.250 ppb on September 12, and in Indian Creek from 42 ppb in June 9 to 0.300 ppb on August 25. The finished water supply of Cedar Rapids contained 0.483 ppb; Davenport, 0.405; Iowa City, 0.20; and Des Moines, 0.03 ppm. These seasonal changes in Atrazine content in water reflect agricultural runoff following spring preemergence application. All the water examined in Iowa contained atrazine.

Propazine, Simazine and Cyanazine were also detected in finished water in the U.S. (USEPA, 1976d).

II. METABOLISM

In animals, the dominant metabolic reaction is N-dealkylation, and rats have produced 20 metabolites from atrazine, including 4-amino-N-ethyl-, 4-amino-N-isopropyl-, 4,6-diamino-, 4-amino-N-acetyl-, and 4-amino-N-isopropionyl-2-chloro-s-triazines. Rabbits also excreted N-(chloro-4-amino-s-triazinyl-6)-glucoside (Menzie 1969). No firm evidence of ring cleavage has been found in degradation studies with bacteria, plants, or animals.

Cyanazine degradation proceeds initially by hydrolysis of the nitrile group and slower hydrolysis of the 2-chloro group. 2-Hydroxycyanazine is the major metabolite found in rat feces. The rat also produces the 4-amino derivative and the N-acetylcysteinyl derivative and hydrolyzes the cyano group to the corresponding amide and carboxy derivatives (Menzies, 1974).

In a laboratory model ecosystem study, with carbon-14 ring-labeled Atrazine, the environmental degradation products were 2-amino-4-chloro-6-isopropylamino-s-triazine and 2-amino-4-chloro-6-ethylamino-s-triazine. There was only a slight degree of food-chain transfer of Atrazine (ecologic magnification 11 x in fish) or any of its degradation products (Metcalf and Sanborn, 1975).

Simazine residues from water treated at 2.5 ppm rose to a maximum of 2.2 ppm in bluegill after 28 days and declined to 0.76 ppm after 60 days; in bass, they rose to 1.50 ppm after 28 days and declined to 0.88 ppm after 60 days (USEPA, 1976c).

III. HEALTH ASPECTS

A. Observations in Man

No case of poisoning in man from Simazine, Atrazine, Propazine, or Cyanazine has been reported, although exposure to Simazine has caused acute and subacute dermatitis in the U.S.S.R., characterized by erythema, slight edema, moderate pruritus, and burning lasting 3 - 5 days (Elizarov, 1972).

B. Observations in Other Species

Acute Toxicity. The acute oral toxicity of Simazine in rats, mice, rabbits, chickens, and pigeons was 5,000->5,000 mg/kg. The acute dermal toxicity in rabbits was over 0.16 g/kg. For Atrazine, the oral LD_{50} is 3,080 mg/kg in rats and 1,750 mg/kg in mice. For Propazine, the oral LD_{50} is over 5,000 mg/kg in rats and mice. For Cyanazine the oral LD_{50} is 334 mg/kg in rats, and the dermal LD_{50} is over 2,000 mg/kg in rabbits (WSSA, 1974).

Chronic Toxicity. Simazine fed to rats for 2 years at 1.0, 10, and 100 ppm produced no difference between treated and control animals in gross appearance or behavior. The rats fed 100 ppm had approximately twice as many thyroid and mammary tumors as the control animals, but it was stated that these were not attributable to Simazine (USEPA, 1976c).

Propazine at 250 mg/kg for 130 days produced no gross signs of toxicity or pathologic changes (WSSA, 1974).

Atrazine, in 2-year chronic-feeding studies at 100 ppm in the diet of rats, produced no gross or microscopic signs of toxicity (WSSA, 1974).

Cyanazine in 2-year feeding studies in rats and dogs, showed no signs of toxic effects at levels up to 25 ppm (WSSA, 1974).

A 2-year chronic-feeding study of Simazine in dogs with Simazine 80W fed at 15, 150, and 1,500 ppm showed only a slight thyroid hyperplasia at 1,500 ppm and slight increases in serum alkaline phosphatase and serum glutamic oxalacetic transaminase in several of the dogs fed 1,500 ppm (USEPA, 1976c).

Mutagenicity. Simazine and Atrazine were inactive in a standard mutagenicity screen with microorganisms, e.g., Simazine was negative with four strains of *Salmonella typhimurium* (USEPA, 1976c). Plewa and Gentile (1975) demonstrated that extracts of maize seedlings grown on soil treated with Atrazine at recommended rates contain an agent that is highly mutagenic in *Saccharomyces cerevisiae* (D4). Further study (Gentile and Plewa, 1976) has shown that the kernels of maize grown on Atrazine-treated plots contain this mutagenic agent, which produces mutation rates up to 30 times that of untreated maize. These data strongly suggest that maize plants can metabolize Atrazine into a mutagenic agent and generate considerable concern about ubiquitous triazine residues in water supplies.

Carcinogenicity. Atrazine, Propazine and Simazine were fed to 2 strains of mice at 21.5, 46.4 and 215 mg/kg/day respectively for 80 weeks (Innes *et al.*, 1969). The incidences of hepatomas were: 4.24% in controls, 5.6% in Atrazine treated, 5.7% in Propazine treated, and 5.6% in Simazine treated.

Reproduction. Simazine at 50 and 100 ppm in the diet had no adverse effects on reproduction of rats or offspring over three generations (USEPA, 1976c). Similar experiments with chickens and quail showed anomalies in the urogenital tracts of male chickens when eggs were sprayed with 0.5, 0.7, 1.0, and 1.5% aqueous solutions of Simazine (Didier and Lutz-Ostertag, 1972).

Teratogenicity. No available data.

V. CONCLUSIONS AND RECOMMENDATIONS

Atrazine, Propazine and Simazine all appear to have low chronic toxicity. The only good carcinogenicity feeding study done on these compounds did not reveal a significant increase in cancer incidence over controls. On the basis of these chronic studies an ADI was calculated for each of these compounds. The ADI for Atrazine is 0.0215 mg/kg/day, for Propazine 0.0464 mg/kg/day, and for Simazine 0.215 mg/kg/day. The available chronic toxicity data for Atrazine, Simazine and Propazine are summarized in Table VI-10.

TABLE VI-10. Summary of Chronic Data for Atrazine, Simazine and Propazine

Species	Duration of study	Dosage levels	Highest no-adverse effect level or lowest minimal effect level	Effect Measured	Reference
Simazine					
Rat	2 yrs.	0 1.0 ppm 10 ppm 100 ppm		tumors 13.9% tumors 50%	Cited in EPA 1976a,
Rat	8 mths.	10 mg/kg/day 20 mg/kg/day 100 mg/kg/day		av. length life 200 days av. length life 151 days av. length life 126 days	Cited in EPA 1976a
Dog	2 yrs.	0 12 ppm 120 ppm 1,200 ppm	≤ 12 ppm	thyroid/body ratio 0.006 thyroid/body ratio 0.009 thyroid/body ratio 0.009 thyroid/body ratio 0.011	Cited in EPA 1976a
Mouse	80 wks.	0 215 mg/kg/day	≤ 215 mg/kg/day[a]	Hepatoma 4.2% Hepatoma 5.6%	Innes et al., 1969
Atrazine					
Mouse	80 wks.	0 21.5 mg/kg/day	21.5 mg/kg/day[b]	Hepatoma 4.2% Hepatoma 5.0%	Innes et al., 1969
Propazine					
Mouse	80 wks.	0 46.4 mg/kg/day	46.4 mg/kg/day[c]	Hepatoma 4.2% Hepatoma 5.7%	Innes et al., 1969

Using an uncertainty factor of 1,000, suggested no-adverse-effect level for Simazine in drinking water is calculated as follows:

$$\frac{215}{1000} = 0.215 \text{ mg/kg/day (ADI)},\ 0.215 \times 70^{d} \times 0.1^{e} = 1.505 \text{ mg/liter}$$

Using an uncertainty factor of 1,000, suggested no-adverse-effect level for Atrazine in drinking water is calculated as follows:

$$\frac{21.5}{1000} = 0.0215 \text{ mg/kg/day (ADI)},\ 0.0215 \times 70^{d} \times 0.1^{e} = 0.15 \text{ mg/liter}$$

Using an uncertainty factor of 1,000, suggested no-adverse-effect level for propazine in drinking water is calculated as follows:

$$\frac{46.4}{1000} = 0.0464 \text{ mg/kg/day (ADI)},\ 0.0464 \times 70^{d} \times 0.1^{e} = 0.32 \text{ mg/liter}$$

[a,b,c] Test studies from which to calculate suggested no-adverse-effect level.

[d] Assume average weight of human = 70 kg.

[e] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

5. URACIL

BROMACIL

I. INTRODUCTION

Bromacil, or 5-bromo-3-sec-butyl-6-methluracil, is one of several substituted uracils that were introduced as broad-spectrum herbicides in 1972. Trade names include Hyvar, Provar (Bromacil plus Diuron), and Isocil (Spencer, 1973). It is estimated that 3 million pounds of this agent was used in the United States in 1972 (Von Rumker et al., 1975) and 8 million pounds was produced in 1971 (NAS, 1975).

Bromacil is used primarily for the control of annual and perennial grasses and broadleaf weeds, both nonselectively on noncrop lands and selectively for weed control in a few crops (citrus and pineapple). It appears to act in plants by inhibiting photosynthesis and to be primarily absorbed thru the roots.

Bromacil is manufactured by the reaction of phosgene and ammonia with sec-butylamine to produce sec-butylurea, which reacts with ethylacetoacetate to produce 3-sec-butyl-6-methyluracil, which is then brominated to produce Bromacil (USEPA, 1975a).

Bromacil is soluble in water at 815 ppm at 25°C, and it is stable in water, aqueous bases, and common organic solvents. It decomposes slowly in strong acids (USEPA, 1975a).

Bromacil undergoes photochemical decomposition and is degraded in soil. The degradation in soil appears to follow first-order kinetics and to be nonenzymatic. However, Bromacil is subject to microbial decomposition under moist soil conditions (USEPA, 1975a).

II. METABOLISM

Bromacil is absorbed from the gastrointestinal tract and appears to be excreted primarily in the urine. The major metabolite in rodents and man is 5-bromo-3-sec-butyl-6-hydroxymethyluracil, which can be detected as a glucuronide conjugate. Other minor metabolites include 5-bromo-3-(2-hydroxy-1-methylpropyl)-6-methyluracil, 3-sec-butyl-6-hydroxymethyluracil, 5-bromo-3-(3-hydroxy-1-methylpropyl)-6-methyluracil, and an unidentified bromine-containing compound (Gardiner et al., 1969). 5-Bromouracil was not found in hydrolysed or nonhydrolysed urine samples from humans exposed to Bromacil (USEPA, 1975a).

III. HEALTH ASPECTS

A. Observations in Man. No available data.

B. Observations in Other Species

Acute Effects. The acute oral LD_{50} of Bromacil in rats is 5,200 mg/kg, and the acute inhalation toxicity is greater than 4.8 mg/liter per 4 h. The acute dermal toxicity of Bromacil was estimated to be at 5,000 mg/kg in rabbits. Application of Bromacil (80% wettable powder) to abraded guinea pig skin produced only mild irritation, without evidence of induced skin sensitization. Because Bromacil causes emesis in dogs, its acute oral toxicity has not been determined in this species, but oral doses of 250 mg/kg produce toxicity (weight loss or abnormal gait) in sheep, chickens, and cattle. Toxic symptoms in poisoned animals also include anorexia, depression, tympanites (in cattle and sheep), and increased respiratory rate (in dogs) (USEPA, 1975a).

Subchronic and Chronic Effects. Male rats were given Bromacil (as a 15% aqueous solution of the 80% AI wettable powder) for 2 weeks (5 days/week) at 650, 1,035, and 1,500 mg/kg. There were six animals in each dose group; five rats died after five doses at the highest dosage level, and one died after 10 doses at the intermediate dosage. There were no deaths in the low-dosage group, but these animals exhibited focal cell hypertrophy and hyperplasia of the liver, which were also seen in the higher-dosage groups. In another subchronic study in which 10 male and 10 female rats were fed Bromacil at 50, 500, 2,500, 5,000, 6,000, and 7,500 ppm for 90 days, there were no signs of mortality or toxicity; but pathologic examination of the tissues from these animals revealed increased thyroid activity in rats fed 5,000 ppm higher (Sapp, 1965). Bromacil (83% AI wettable powder) was also fed to rats for 2 years at 50, 250, and 1,250 ppm. Additional controls in this study were corn-oil-vehicle groups, and there were initially 36 male and 36 female rats per diet group. Rats from each diet group were sacrificed at the end of 3, 6, and 12 months of feeding; weight loss in the female rats fed 1,250 ppm was the only toxic effect observed. Histopathologic examination of the tissues from these rats revealed hyperplasia in the light and follicular cells of the thyroid, and there was a follicular cell adenoma in one of the females fed 1,250 ppm (Sherman et al., 1963). A 2-year feeding study in dogs has also been carried out with Bromacil in which three male and three female dogs were fed 0.005, 0.025, and 0.125% Bromacil. No toxic effects were observed, although one dog (0.005% diet) died from non-Bromacil effects (Hazelton Labs, 1966).

Mutagenicity. The mutagenic potential of Bromacil has been investigated in several studies, because 5-bromouracil is mutagenic. However, 5-bromouracil is not a metabolite of Bromacil, and Bromacil was not found to be mutagenic in any of these tests (USEPA, 1975a).

Carcinogenicity. No available data.

Reproduction. No significant reproductive effects were observed in a two-generation rat study in which indexes of fertility, gestation, viability, and lactation were observed. The dosages for these studies were 50, 250, 1,250 ppm, and there were 12 male and 12 female rats in each group (USEPA, 1975a).

No gross manifestations of teratogenic effects were observed in the fetuses of rabbits fed Bromacil in the diet at 50, 250, 1,250 ppm (USEPA, 1975a).

IV. CONCLUSIONS AND RECOMMENDATIONS

Bromacil is low in both acute and chronic toxicity. It appears that 1,250 ppm is a no-adverse-effect dietary concentration of Bromacil in dogs. However, rats fed this concentration of Bromacil in the diet exhibited abnormal thyroid pathology. In a 2-year feeding study the no-adverse-effect dose for rats was 12.5 mg/kg/day. Based on these data an ADI was calculated at 0.0125 mg/kg/day. The available data on chronic oral toxicity and calculations of ADI are summarized in Table VI-11.

TABLE VI-11: Summary of Subchronic and Chronic Toxicity Data for Bromacil

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Rat	14 days	0-1500 mg/kg/day 6 animals per group	650 mg/kg/day	liver hyperplasia	Sapp, 1965
Rat	90 days	0-7000 ppm, 20 animals per group	2500 ppm (125 mg/kg/day)[d]	no toxic effect	Sapp, 1963
Rat	2 years	0-1250 ppm, 72 animals per group	250 ppm[c,d] (12.5 mg/kg/day)	no toxic effect	Sherman, 1965
Dog	2 years	0-0.125% of Bromacil 8 animals per group	0.125% (31 mg/kg/day)[d]	no toxic effect	Hazelton Labs, 1966

Using an uncertainty factor of 1000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{12.5}{1000} = 0.0125 \text{ mg/kg/day (ADI)}, \quad 0.0125 \times 70^{a} \times 0.1^{b} = 0.088 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Test study from which to calculate suggested no-adverse-effect level.

[d] Assume weight of rat = 0.4 kg and of dog = 10 kg; assume average daily intake food consumption of rat = 0.02 kg and of dog = 0.25 kg.

6. BIPYRIDYL

PARAQUAT

1. INTRODUCTION

Paraquat, or 1,1'-dimethyl-4,4'-dipyridylium, is a general weed-killer of the bipyridyl family of herbicides. It is available either as a dichloride or as a dimethysulfate salt. Both compounds are water-soluble. It is registered as a contact herbicide for noncrop use.

During recent years paraquat has been used extensively in California - 374,009 lbs in 1973, and 272,361 lbs in 1974. In 1975, 248,070 lbs were used during the first three quarters of the year (University of California Pesticide Data Bank, 1975). It is used primarily for general weed control and as a desiccant.

Paraquat kills plants by acting on the green parts, not on woody stems, and is rapidly inactivated by contact with clay in the soil. Apparently, the molecule itself can penetrate into the crystal lattice of clay minerals, where it is firmly bound by physical bonding (Hayes _et al._, 1975). Under these circumstances, paraquat cannot be attacked by soil microorganisms, because they cannot penetrate the lattice. In the bound form, paraquat is biologically inert, and it has been demonstrated that it does not cause any harm to either plant or animal life. When paraquat is in an environment that does not have clay particles, it is readily degraded by microorganisms. Under these circumstances, it is generally accepted that paraquat is environmentally safe, because its associated toxicologic hazard presents no major problems.

Apparently, paraquat is not extensively metabolized in plants; it has been demonstrated that there is no metabolic breakdown of paraquat in tomato, broad bean, and maize (Weed Science Society of America, 1974). The herbicidal activity and organic chemical reactions of paraquat formulations depend solely on the paraquat cation and are not influenced by the nature of the associated anion, because the salts are largely dissociated in aqueous solution.

Paraquat is readily decomposed by ultraviolet light. Two major decomposition products are 1-methyl-4-carboxypyridinium ion (Funderburk _et al._, 1966) and methylamine hydrochloride. Experiments have demonstrated that paraquat solutions degrade rapidly in ultraviolet light, with very little remaining after 48 h of exposure.

II. HEALTH ASPECTS

A. Observations in Man

Paraquat is acutely toxic to man. As a result, many accidental and suicidal deaths have been reported (Kimbrough, 1974; Copland et al., 1974; van Dijk et al., 1975; Carson, 1972; Beebeejaun et al., 1971). It has been estimated that a lethal dose in man is about 14 ml of a 40% solution of paraquat (Kimbrough, 1974). The symptoms of poisoning include burning of the mouth and throat, nausea and vomiting, respiratory distress, and transient effects on the kidneys, heart, and nervous system. Death is usually due to progressive fibrosis and epithelial proliferation in the lungs.

Dermal exposure to paraquat concentrates may result in severe skin irritation; while nosebleeds may result from exposure of the nasal mucosa; and several severe eye injuries have resulted from eye exposure. Absorption studies have shown that paraquat is readily absorbed through the skin of both humans and animals.

There is no effective antidote for paraquat poisoning in man, although a few patients have recovered after ingesting doses thought to be fatal (Jones and Owen-Lloyd, 1973; Galloway and Petrie, 1972).

B. Observations on Other Species

Acute Effects. Paraquat is acutely toxic to both man and animals. The oral LD_{50} reported in rats is 110 - 173 mg/kg (Mehani, 1972; Murry and Gibson, 1972). In the mouse, the LD_{50} is 90 - 120 mg/kg. The LD_{50} in monkeys is 50 mg/kg, and in guinea pigs it is 22 mg/kg (Murry and Gibson, 1972).

Animals poisoned by inhalation do not show major damage to the lungs, as is usually found when paraquat is administered orally. Apparently, it acts similarly to a powerful irritant, such as phosgene, and the changes in the lung are typical of such effects. Death at sufficiently high doses occurs within a short period, and animals that do not die within this period recover completely; delayed fibrosis does not occur (Conning, 1969).

Chronic Effects. Two-year feeding studies with rats have shown that paraquat at up to 170 ppm in the diet does not produce significant abnormalities in any of the several characteristics investigated (Chevron Chem. Co., 1975). Dogs fed paraquat at 7.2 and 34 ppm in the diet over a period of 27 months have not developed significant abnormalities. However, some changes were observed at 85 and 170 ppm.

Kimbrough and Gaines (1970) have conducted 90-day feeding studies in rats with dietary paraquat concentrations of 100, 400, 500, 600, and 700 ppm. Clinical signs of acute and chronic poisoning included diarrhea, wheezing, irregular and rapid breathing, and red stains around the snout. All animals that died showed morphologic changes in their lungs.

Mutagenicity. No available data.

Carcinogenicity. No available data.

Reproduction and Teratogenicity. Administration of paraquat to mice, at 1.67 and 3.35 mg/kg intraperitoneally or 20 mg/kg orally, daily on days 8-16 of gestation induced no significant teratogenic effects, although a slight increase in nonossification of sternebrae was observed (Bus et al., 1975). The same investigators reported that, when paraquat was administered to rats on single days of gestation, an average of 7.6% of the fetuses were found dead or being resorbed. Radioactivity reaching the mouse embryo after intraperitoneal or oral administration of (^{14}C)Paraquat on the eleventh day of gestation was low.

III. CONCLUSIONS AND RECOMMENDATIONS

Paraquat is a highly effective, general herbicide that is acutely toxic to man and animals in its concentrated form (20% liquid concentrate). Oral exposure to high doses of paraquat frequently results in death, which is usually due to progressive fibrosis and epithelial proliferation in the lungs. However, in 2-year feeding studies in rats, paraquat did not produce any significant abnormalities.

Paraquat is rapidly inactivated by contact with clay particles in soil and is firmly bound physically. In this form, it is biologically inactive and apparently does not have any immediate or prolonged harmful effects. Thus, it is unlikely that paraquat would be found in large amounts in drinking water. Based on a 2-year feeding study in rats, an ADI was calculated at 0.0085 mg/kg/day. The available toxicity data and calculations of ADI are summarized in Table VI-12.

TABLE VI-12; Summary of Chronic Oral Toxicity Data for Paraquat

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Rat	90 days	300-700 ppm, 10 females per group	300 ppm (15 mg/kg/day)[d]	diarrhea, irregular and rapid breathing	Kimbrough and Gaines, 1970
Rat	27-57 days	250 ppm		death in some cases	Clark, *et al.*, 1966
Rat	2 years	170 ppm	170 ppm (8.5 mg/kg/day)[c,d]	no adverse effect	Chevron Chemical Company, 1975

Using an uncertainty factor of 1000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{8.5}{1000} = 0.0085 \text{ mg/kg/day (ADI)}, \quad 0.0085 \times 70^{a} \times 0.1^{b} = 0.06 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse-effect level.

[d] Assume weight of rat=0.4 kg and average daily food consumption of rat=0.02 kg.

7. DINITROANILINE

TRIFLURALIN, NITRALIN AND BENEFIN

I. INTRODUCTION

The dinitroaniline herbicides are an important group of compounds whose use is expanding. The most prominent member of the group is trifluralin, or α,α,α-trifluoro-2,6-dinitro-*N*-dipropyl-*p*-toluidine (Treflan) which was first marketed in 1963 for use on cotton. It is now registered on more than 50 crops. Other members of the group that have been used include nitralin, or 4-(methylsulfonyl)-2,6-dinitro-*N*,*N*-dipropylaniline (Planavin), and benefin, or *N*-butyl-*N*-ethyl-α,α,α-trifluoro-2,6-dinitro-*p*-toluidine (Balan). A summary of dinitroaniline compounds used or under development as herbicides is given by Helling (1976). These compounds are particularly effective against annual grasses and some broadleaf weeds.

It is estimated (NAS, 1975) that 11.4 million pounds of trifluralin and 2.7 million pounds of nitralin were used in the United States in 1971. Virtually all of this material was used in agriculture. Another estimate (Helling, 1976) indicates the consumption of about 17 million pounds of trifluralin in the United States in 1972. About 60% of the material is used on soybeans, 30% on cotton, and 10% on other crops. Most of the use is in the north central and south central states, especially Illinois, Iowa, and Mississippi, which consume about three-fourths of the total production. The dinitroaniline herbicides probably account for 5 - 10% by volume domestic herbicide use. Because trifluralin is by far the most important member of this group, with respect to total volume of use, this report will concentrate on it, with some supporting information on several others.

Trifluralin is synthesized by the reaction of *p*-chlorobenzotrifluoride with fuming nitric acid to produce 3,5-dinitro-4-chlorobenzotrifluoride, which then reacts with di-*n*-propylamine to produce trifluralin. The technical material contains the desired product at more than 95%. It is soluble in water at 0.2 - 0.4 ppm at 25°C.

The dinitroanilines are strongly adsorbed by soil and moderately persistent in soil.

In the annual Market basket Surveys conducted by the Food and Drug Administration, trifluralin residues have never been detected (Corneliussen, 1970, 1972; Manske and Corneliussen, 1974). Trifluralin is tolerated at 0.05 ppm by most crops; exceptions are alfalfa hay (0.2 ppm), carrots (1 ppm), and mung beans (2 ppm). The FAO/WHO has not established an acceptable daily intake of trifluralin or any other dinitroaniline herbicide.

Trifluralin was detected in finished water in the U.S. (USEPA, 1976d).

II. METABOLISM

Studies on the metabolism of trifluralin have been rather limited. Emmerson and Anderson (1966) studied the metabolism of trifluralin in rats and dogs. Approximately 80% of the ingested compound was excreted in the feces, the remainder in the urine. Analysis of the feces revealed the parent compound and one metabolite, the amino derivative resulting from reduction of one nitro group. Ten different materials in the urine were separated by thin-layer chromatography. Only three were identified; they were the products of nitro reduction or removal of one or both propyl groups.

Several investigators have reported on the behavior of trifluralin in dairy animals (Fisher *et al.*, 1965; Golab *et al.*, 1969; Williams and Feil, 1971). Trifluralin is dealkylated in the rumen, losing one or both propyl groups; the nitro groups are reduced to one or two amino groups. The two types of reactions occur simultaneously, leading to a trifluoromethyltriaminobenzene. Unidentified polar products were also produced in rumen fluid. The acute toxicity of some of these metabolites has been determined. Metabolites with free amino groups tend to be somewhat more acutely toxic in test species, although the maximal toxicity is still quite low, at 1,803 mg/kg for the diamino compound in the mouse.

Nelson *et al.* (1976) studied three structurally related dinitroaniline herbicides--trifluralin, profluralin, and fluchloralin--in rat hepatic microsomal systems. All three were extensively metabolized by both normal and phenobarbital-induced microsomal systems. Identification of the metabolites extractable with ethylacetate from the aqueous incubation mixtures indicated that aliphatic hydroxylation of the *N*-alkyl substituents, *N*-dealkylation, reduction of a nitro group, and cyclization to form benzimidazoles (and, in the case of fluchloralin, a quinoxaline) were the predominant metabolic routes for these herbicides *in vitro*. Of particular interest was the formation of the benzimidazole metabolites.

III. HEALTH ASPECTS

A. Observations in Man

No controlled studies have been conducted with dinitroaniline compounds in humans. Since 1965, 16 episodes of trifluralin poisoning have been reported. There have been no fatalities, and only one case required hospitalization. Ten of the 16 cases involved symptoms that appeared to be related to the solvent, rather than trifluralin itself. In general, adverse effects of dinitroaniline herbicides in humans have been few and minor (Verhulst, 1974).

B. Observations in Other Species

Acute Effects. The dinitroaniline herbicides are very low in acute toxicity. The following oral LD_{50} values have been reported for various dinitroaniline compounds in rats: technical trifluralin, greater than 10,000 mg/kg; benefin, greater than 10,000 mg/kg; nitralin, greater than 6,000 mg/kg (Berg, 1976). The acute oral LD_{50} of the trifluralin emulsifiable concentrate formulation in rats is 3,700 mg/kg.

The acute oral toxicity of dinitroanilines in other animals is similarly low. The oral LD_{50} of trifluralin in mice is 5,000 mg/kg; of nitralin, greater than 2,000 mg/kg (Berg, 1976). The acute oral LD_{50} of trifluralin in dogs, chickens, and rabbits is greater than 2,000 mg/kg.

The dermal LD_{50}'s of trifluralin and nitralin in rabbits were greater than 2,000 mg/kg after 25 h of exposure (Worth, 1970). Rabbits exposed to 500 mg of technical trifluralin in a standard Draize skin irritation study had a score of zero, indicating no dermal irritation (Worth, 1970). Technical trifluralin also caused no damage when tested in rabbit eyes.

Subchronic and Chronic Effects. Chickens, which are sensitive to the cataractogenic properties of compounds, were exposed to trifluralin. There was no effect in the trifluralin-treated chickens, whereas 14 of the 16 chickens in the positive control had obvious lens opacities by the third day of the study conducted by Worth (1970).

In a 10-day study of cattle, sheep, and chickens orally treated with trifluralin, benefin, and nitralin, the no-adverse-effect dosage was 100 mg/kg/day for trifluralin in cattle, sheep, and chickens. For benefin, poisoning and changes were observed at 25 mg/kg/day in cattle and 50 mg/kg/day in sheep and chickens. For nitralin, poisoning and death were observed at 250 mg/kg/day in cattle and 375 mg/kg/day in sheep; the no-adverse-effect dosage was 500 mg/kg/day in chickens (Palmer, 1972).

Harlan rats (six males and six females in each group) were fed technical trifluralin at 20, 200, 2,000, and 20,000 ppm in the diet for 2 years. At the highest dosage level, rats showed significant growth retardation and bile duct proliferation and survived a maximum of 460 days. In all other groups, there were no significant differences between treated animals and controls in growth, mortality, food intake, efficiency of food utilization, gross pathologic effects, and microscopic examination of major organs and tissues. The no-adverse-effect dosage, therefore, was established as 2,000 ppm, which is equivalent to approximately 100 mg/kg/day, according to Elanco (1967). However, with the assumptions on food consumption and animal weight of this report, 2,000 ppm is equivalent to 333 mg/kg/day.

Another 2-year study was conducted with 25 male and 25 female Cox rats fed trifluralin at 200, 1,000, and 2,000 ppm trifluralin. Several male rats at the two higher dosages exhibited enlargement of the thyroid. Two male rats at 1,000 ppm and one male at 2,000 ppm had pheochromocytomas. Neither of these responses was dosage-related. Hence, the no-adverse-effect dosage was reported to be 2,000 ppm (Elanco 1967).

Three studies on the chronic toxicity of trifluralin in dogs have been conducted. In one, eight mongrel dogs were given daily oral doses in capsules over a 2-year period. One male and one female in each group were given 2.5 mg/kg, 5 mg/kg, and 25 mg/kg. Two females were given 10 mg/kg. There were no adverse effects at any dosage. In another study, beagles were treated at 1, 2.5, 5, and 10 mg/kg. With two animals per group (except for the lowest, which included four animals), no adverse effects were found at any dosage. In a 3-year study, purebred beagles were given trifluralin orally at 10 and 25 mg/kg. Each treatment group included two animals of each sex, and a control group was established with three animals of each sex. At 25 mg/kg, an increased liver:body-weight ratio was observed. Therefore, the no-adverse-effect dosage was considered to be 10 mg/kg (Worth, 1970).

Two-year feeding studies of nitralin in rats and dogs have been conducted by the Stanford Research Institute (Burdett, 1968a, b). At dietary concentrations of 2.5, 10, 40, 160, and 2,000 ppm in both male and female rats, no adverse effects were found. Therefore, the no-adverse-effect dosage of nitralin is at least 2,000 ppm (333 mg/kg/day). Nitralin was also fed to 10 male and 10 female beagles in the diet at 2.5, 10, 40, 160, and 2,000 ppm for 2 years. No-adverse effects were seen at any dosage. Measured were weight gain, hematologic values, serum alkaline phosphatase levels, blood urea nitrogen, organ weight ratios between experimental animals and controls, and histopathology. Again, the no-adverse-effect dosage is at least as high as 2,000 ppm (40 mg/kg/day).

Mutagenicity. In a large screening study of many herbicides, Anderson *et al.* (1972) noted that trifluralin did not induce point mutations in any of three microbial systems.

Carcinogenicity. There are no reports of carcinogenic or tumorigenic effects of trifluralin or other dinitroaniline herbicides.

Reproduction. Groups of six male and 12 female rats were fed trifluralin in the diet at 200 and 2,000 ppm in a four-generation reproduction study. There was a definite decrease in the fertility of the animals at 2,000 ppm in the third generation. There were also adverse effects on viability and lactation in the third generation. This was not the case at 200 ppm. The no-adverse-effect dosage, therefore, was 200 ppm in the diet, equivalent to 20 mg/kg/day (Elanco, 1967).

The dogs used in the chronic 3-year study were interbred with animals in their same treatment group. Dosages were 10 and 25 mg/kg/day. A number of experimental difficulties in the study complicated interpretation of the results; however, the no-adverse-effect dosage was stated to be 10 mg/kg/day.

Teratogenicity. Rats, dogs, and rabbits revealed no significant teratogenic effects in offspring (Elanco, 1967). In the dog study, one runt was produced at the highest dosage, but no other abnormalities or malformations were seen in any of the dogs at any dosage. In rabbits, at 1,000 mg/kg/day there was a significant reduction in weight during pregnancy of the does, which did not occur in the control group. At one of the intermediate dosages two of six fetuses had underdeveloped hind legs and hindquarters. This effect was not seen at higher dosages or in controls. Hence, it is not considered to be due to trifluralin.

IV. CONCLUSIONS AND RECOMMENDATIONS

The dinitroanilines are an increasingly important group of herbicides with an extremely low degree of toxicity in mammals. Trifluralin has been used in relatively large amounts in agriculture in the past, and its use is expected to increase. In addition, extensive development of other compounds in this group is underway. The group is likely to include a number of important herbicides in agricultural use for the foreseeable future.

The mode of action of the dinitroanilines has not been delineated at the cellular or molecular level in either plants or animals, although inhibition of mitosis has been observed in plants. No specific characteristic of dinitroaniline poisoning is observed in mammals. Hence, the toxicology of these compounds has been studied in laboratory animals with rather nonspecific indicators for the measurement of toxic end points.

Adequate studies of mammalian toxicity have been reported only for trifluralin, benefin, and nitralin. Fortunately, studies of the acute toxicity of other representatives of the group indicate that the toxicity of the various newer compounds is likely to be about the same. Conclusions on the safety of new compounds can probably be based on studies of trifluralin with some assurance of the reasonableness of extrapolation. The toxicology of the dinitroanilines appears to be straightforward; no reports indicate mutagenic or carcinogenic effects of these compounds. A single report on teratogenicity did not seem to show dose dependence and therefore could not place blame specifically on trifluralin. A no-adverse-effect dosage can thus be set for trifluralin that could be extended without difficulty to include all dinitroaniline herbicides that are structural analogues. The available data on chronic toxicity and a calculated ADI of 0.1 mg/kg/day are summarized in Table VI-13. This concentration can be easily detected in water by a number of analytic techniques.

In light of the recent report of benzimidazole metabolites from dinitroanilines and the vintage of in vivo metabolic studies, there is a need for additional studies on the metabolism of these compounds in mammalian systems. The toxicology of metabolites should be investigated. As new compounds are introduced for development, chronic toxicologic studies should be done, to be sure that no anomalous effect will be observed from them that could not have been predicted from previous work with trifluralin, benefin, and nitralin. Additional studies on the possibility of teratogenic effects of dinitroanilines need to be conducted.

TABLE VI-13: Summary of Chronic Toxicity Data for Trifluralin

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Rats	2 years	20-20000 ppm, orally, 12 animals per group	2000 ppm	no-adverse effect	Elanco, 1976
Rats	2 years	200-2000 ppm, orally, 50 animals per group	2000 ppm	no-adverse effect	Elanco, 1976
Dogs	2 years	2.5-25 mg/kg/day, orally, 8 animals per group	25 mg/kg/day	no-adverse effect	Elanco, 1976
Dogs	2 years	1-10 mg/kg/day 2 animals per group	10 mg/kg/day	no-adverse effect	Elanco, 1976
Dogs	3 years	10 & 25 mg/kg/day, orally, 4 animals per group	10 mg/kg/day[c] 25 mg/kg/day	no-adverse liver to body-weight ratio	Worth, 1970
Rats	4 generation	0-2000 ppm in diet	200 ppm	no-adverse effect	Elanco, 1967
		18 animals per group	2000 ppm	fertility, viability of offspring, lactation	

Using an uncertainty factor of 100, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{10}{100} = 0.1 \text{ mg/kg/day (ADI)}, \quad 0.1 \times 70^{a} \times 0.1^{b} = 0.7 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Test study from which to calculate suggested no-adverse-effect level.

8. ALDEHYDE

ACROLEIN

I. INTRODUCTION

Acrolein, or acrylaldehyde, is a colorless liquid, readily soluble in water. It is extremely volatile, and vapors of the compound are irritating and cause excessive lacrimation. Dilute solutions of Acrolein are effective in killing undesirable plant life in irrigation streams and ditches.

Acrolein is reportedly a common air pollutant arising from various manufacturing processes and is also a constituent of cigarette smoke (Sinkuvene, 1970).

II. METABOLISM. No available data.

III. HEALTH ASPECTS

A. Observations in Man. No available data.

B. Observations in Other Species

Acute Effects. The acute oral LD_{50} of aqueous Acrolein solutions is 42 mg/kg in rats and 28 mg/kg in mice (Newell, 1958). Water intake of male rats receiving Acrolein at 80 and 160 ppm and female rats receiving 160 ppm was markedly decreased. Dietary consumption of the male rats was decreased slightly at 160 ppm, whereas that of the females was unaffected.

Subchronic and Chronic Effects. In a subchronic study conducted with male and female rats for 90 days, Acrolein was added to the drinking water at 5, 13, 32, 80, and 200 ppm. No hematologic, organ-weight, or pathologic changes could be attributed to the ingestion of Acrolein. However, water consumption was reduced by one-third at 200 ppm for the first 3 weeks. By the twelfth week, the animals had apparently adapted to the odor and taste of the Acrolein (Newell, 1958).

Three additional groups of male rats were given drinking water containing Acrolein at 600, 1,200, and 1,800 for 60 days. Only one of five animals died at 600 ppm, whereas all the animals died at 1,200 and 1,800 ppm (Newell, 1958). Death was apparently due to lack of water intake; they would not drink the unpalatable solutions. Tissues from the surviving animals 600 ppm did not show any gross or micropathologic abnormalities.

No chronic-toxicity studies are available.

Inhalation Toxicity. A study by Watanabe and Aviado (1974) has indicated that mice that inhale Acrolein at 0.1 μg/ml daily for 5 weeks develop reductions in pulmonary compliance. Because mice that had been exposed to the vapor phase of cigarette smoke do not exhibit reduced pulmonary compliance, it was concluded that the amounts of Acrolein contained in cigarette smoke contribute little to compliance changes.

Inhalation studies with mongrel dogs have revealed that total-tract retention of Acrolein is about 81% when the animals were exposed to concentrations of 0.4-0.6 μg/ml (Egle, 1972). The daily average maximal permissible concentration of Acrolein in the atmosphere has been determined in rats (Gusev, 1966). For these studies, groups of rats were placed in gas chambers containing Acrolein at 0.01, and 1.52 mg/m³ for periods of a few days to several weeks. Various factors were measured, but there was considerable lung damage in the group exposed to 1.52 mg/m³. It was concluded that 0.1 mg/m³ should not be exceeded. In another study, the maximal one-time and daily average permissible concentrations of Acrolein in the atmosphere were recommended to be set at 0.03 mg/m³ (Sinkuvene, 1970).

Other Toxicologic Effects. Murphy (1965) demonstrated that Acrolein affects liver alkaline phosphatase and tyrosine - α - ketoglutarate transaminase activities in rats 5-12 h after injection (3 mg/kg 20 h before sacrifice) or inhalation of Acrolein. Murphy found that these effects could be prevented or substantially reduced by prior adrenalectomy or hypophysectomy or by pretreatment of the animals with chemicals that inhibit protein synthesis. According to Murphy, the data suggested that the irritant action of Acrolein stimulates the pituitary-adrenal system, leading to hypersecretion of glucocorticoids that act to induce or stimulate the synthesis of increased amounts of the enzyme proteins by the liver.

Studies have been conducted on the effect of Acrolein on DNA-dependent DNA polymerase of regenerating rat liver. Munsch et al. (1973) found that an Acrolein-enzyme interaction seems to be fully responsible for the impaired replication in vitro, whereas incubations of the substrates with Acrolein slightly but reproducibly increase the enzyme activity, and incubations of the template with Acrolein do not affect the duplication. When DNA polymerase was preincubated with increasing amounts of Acrolein, the template duplication was either activated at low molarities or inhibited above 8×10^{-5}M.

Acrolein appears to possess indirect sympathomimetic activity. It produced irreversible contractile responses in rat vas deferens that were not blocked by reserpine pretreatment (Beckner et al., 1974). Acrolein also apparently interacts with tissue norepinephrine stores and affects nonspecific membrane calcium-binding sites.

Mutagenicity, Teratogenicity, and Carcinogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

Acrolein is an herbicide that is used primarily for the control of aquatic weeds. It is highly volatile and apparently does not persist for extended periods in an aqueous environment. Only limited acute- and subchronic-toxicity data are available. In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity and long-term oral toxicity of Acrolein, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

B. INSECTICIDES

1. CHLORINATED HYDROCARBONS

CYCLODIENES: ALDRIN, DIELDRIN, ENDRIN, CHLORDANE, HEPTACHLOR, AND HEPTACHLOR EPOXIDE

I. INTRODUCTION

The cyclodiene insecticides are all derivatives of hexachlorocyclopentadiene produced by the Diels-Alder, or diene, reaction. Their discovery and development date from the synthesis of chlordane by Julius Hyman in 1944 (U.S. Pats. 2,509,160 and 2,606,910). Perhaps 600 million pounds of these highly chlorinated, cyclic organic compounds have been dispersed into the soil, air, water, and food of the United States during the last 30 years. Little is certain about the degradation and fate of these compounds; however, traces of them and their stable epoxide oxidation products are ubiquitous in the environment and are heavily bioconcentrated in the lipids of terrestrial and aquatic wildlife, humans, and foods, especially animal fats and milk.

The cyclodienes have been used principally as preemergence soil insecticides for the control of corn rootworms, wireworms, cutworms, etc.; as seed treatments; as soil poisons for control of termites and ants; and on cotton for the control of the boll weevil and bollworms.

Aldrin, or 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-endo-1,4-exo-5,8-dimethanonaphthalene, is soluble in water at 0.027 ppm at 25C (Gunther *et al.*, 1968).

Dieldrin, or 6,7-epoxy aldrin, is soluble in water at 0.25 ppm at 25°C (Gunther *et al.*, 1968).

Endrin, or 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-*endo*-5,8-dimethanonaphthalene, is soluble in water at 0.25 ppm at 25°C (Gunther *et al.*, 1968). Endrin is produced by condensing hexachlorocyclopentadiene with vinyl chloride to produce heptachlorbicyclo-(2.2.1)-2-heptene. This is condensed with cyclopentadiene to form isodrin and that is oxidized to the 6,7-epoxide with peracetic or perbenzoic acid (Brooks 1974).

Chlordane, or 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene, is a viscous amber liquid soluble in water at about 0.009 ppm at 25°C. Chlordane is manufactured by condensing hexachlorocyclopendadiene with cyclopentadiene to form chlordene and chlorinating the latter to approximate $C10H6Cl8$.

The technical material contains about 60-75% of the *cis*-(m.p. 106.5-108°), and *trans*-(m.p. 104.5-106°) isomers together with unreacted chlordene and isomers of the $C_{10}H_5Cl_7$ product Heptachlor (Brooks 1973).

Heptachlor, or 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4, 7-methanoindene, is soluble in water at about 0.056 ppm at 25°C (Park and Bruce 1968). Heptachlor is produced from Chlordene by chlorination with sulfuryl chloride (Brooks 1973).

Heptachlor epoxide, or 1,4,5,6,7,8,8-heptachloro-2,3-epoxy-3a, 4,7,7a-tetrahydro-4,7-methanoindene, is soluble in water at 0.350 ppm (Park and Bruce 1968).

Domestic production in 1971 estimates are (NAS, 1975): Chlordane, 25 million pounds; Aldrin, 10 million pounds; Heptachlor 6 million pounds; Dieldrin, less than 1 million pounds; and Endrin, less than 1 million pounds. Because of their environmental persistence and carcinogenic behavior in laboratory animals, Aldrin and Dieldrin were banned by the EPA on October 1, 1974, and Chlordane and Heptachlor registrations for agricultural crops were suspended on April 1, 1976.

Because of their persistence the cyclodienes and their epoxides--viz., Dieldrin, Heptachlor epoxide, and probably Oxychlordane--are found in surface waters virtually everywhere. In an extensive 1958-1965 survey of the rivers of the United States, Breidenbach *et al.* (1967) found the following average concentrations of the cyclodienes:

Aldrin, <0.001-0.006 ppb
Dieldrin, 0.08-0.122 ppb
Endrin, 0.008-0.214 ppb
Heptachlor, 0.0-0.0031 ppb
Heptachlor epoxide, <0.001-0.008 ppb
DDT, 0.008-0.144 ppb

The highest concentrations were generally found in the lower Mississippi basin. In 1964, 74% of the grab samples were positive for: Dieldrin, 46% for Endrin, 10% for Aldrin, 17% for Heptachlor, and 25% for Heptachlor epoxide. In comparison, 44% were positive for DDT and 30% for DDE.

More than 500 grab samples of finished drinking water and related raw water from the Mississippi and Missouri Rivers were analysed by Schafer *et al.* (1969). More than 40% of the finished-water samples contained Dieldrin at up to 0.25 ppb, more than 30% contained Endrin, and 20% contained Chlordane at up to 0.5 ppb. Aldrin and Heptachlor were found occasionally.

An extensive investigation of surface, subsurface, and finished water in Iowa (Richard et al., 1974) showed Dieldrin present at the following concentrations:

S. Skunk River	2-76 ppt
Indian Creek	4-30 ppt
Des Moines River	2-12 ppt
Raccoon River	1-12 ppt
Red Rock Reservoir	3-36 ppt
Rathbun Reservoir	2-23 ppt
Cedar Rapids (surface)	42 ppt
Iowa River	22 ppt
Mississippi River	<0.5-7 ppt
Finished water:	
Davenport	2 ppt
Iowa City	5 ppt
Des Moines	0.4-2 ppt

It was concluded that water treatment plants were not removing substantial amounts of pesticides from raw water, even by filtration through activated-carbon beds.

The New Orleans water supply contained Dieldrin at 0.05-0.07 ppb (50-70 ppt) and Endrin at 0.004 ppb (USEPA, 1974a). The 10-city drinking-water survey (USEPA, 1975j) found Dieldrin at 1-2 ppt in drinking water of Miami, Seattle, Ottumwa (Iowa), and Cincinnati. Other cyclodienes identified in U.S. drinking water included Aldrin, Chlordane, Chlordene, Endrin (80 ppt), Heptachlor, and Heptachlor epoxide.

Standards have been proposed for the maximal permissible concentrations of the cyclodienes in finished water (Schafer et al., 1969). Concentrations suggested in 1965-1966 and based on those of the Subcommittee on Toxicology in 1965 were: Aldrin, 32.0 ppb; Dieldrin, 18.0 ppb; Endrin, 1.0 ppb; Heptachlor, 78.0 ppb; Heptachlor epoxide, 18.0 ppb; and Chlordane, 52 ppb. The suggested DDT-T (DDT, DDE, and DDD combined) concentration was 42 ppb. These were drastically lowered in a 1967 recommendation (Ettinger and Mount, 1967) based on maximal reasonable stream allowances to: Aldrin, 0.25 ppb; Dieldrin, 0.25 ppb; Endrin, 0.1 ppb; Heptachlor, 1.0 ppb; Heptachlor epoxide, 1.0 ppb; and Chlordane, 0.15 ppb. The DDT-T allowance was 0.5 ppb.

The U.S. Public Health Service Advisory Committee recommended the following drinking-water standards in 1968 (Mrak, 1969): Aldrin, 17 ppb; Dieldrin, 17 ppb; Endrin, 1 ppb; Heptachlor, 18 ppb; and Heptachlor epoxide, 18 ppb.

The EPA has set an interim standard for Endrin in finished water for 0.0002 mg/liter (USEPA, 1975l).

Residues in Food. The persistent organochlorine cyclodienes are present everywhere in the environment, are readily biomagnified through food chains, and are common trace contaminants of human food. Market Basket Surveys of the U.S. diet, collected in five major U.S. cities and designed to simulate the diet of a 16 - 19-year-old male, have produced results summarized in Table VI-16 (NAS, 1977).

TABLE VI-16: Pesticides in Food

Daily Dietary Intake, mg.

Pesticides	1965	1966	1967	1968	1969	1970	6-Year Average
Aldrin	0.001	0.002	0.001	T*	T	T	0.001
Dieldrin	0.005	0.007	0.001	0.006	0.005	0.005	0.005
Endrin	T	T	T	0.001	T	T	0.001
Heptachlor	T	-	T	T	T	T	T
Heptachlor epoxide	0.002	0.003	0.001	0.002	0.002	0.001	0.002

*T = trace.

The combined residues for Aldrin and Dieldrin are very close to the FAO/WHO acceptable daily intake (ADI) which is 0.0001 mg/kg/day for Aldrin and Dieldrin, vs. 0.00011 mg/kg/day in 1966. For Heptachlor and Heptachlor epoxide, the FAO/WHO ADI is 0.0005 mg/kg/day, vs. 0.00005 mg/kg/day in 1966 (Mrak, 1969). It should be pointed out that recent studies showing increases in mouse hepatomas at the lowest dosages fed--i.e., 0.1 ppm demonstrated that no-adverse-effect level for Aldrin and Dieldrin has never been determined and that the ADI is therefore too high.

Cyclodienes in milk. Residues of the cyclodienes in milk are particularly high because of the ingestion of these insecticides with forage. Dieldrin has the highest retention time of all pesticides in milk, approximately 100 days (Mrak 1969). For example, analyses of 1971 milk samples from 12 grade A dairy farms in an intensive grain-producing area of northwestern Illinois showed combined Aldrin and Dieldrin concentrations in butterfat of 0.1316 - 0.5560 ppm (average 0.2921). There was a definite correlation between the overall Dieldrin soil residue on each farm (0.0104 - 0.1959 ppm) and the concentration in the milk (Moore et al., 1973). Consumption of this milk (composite Dieldrin concentration 0.22 ppm) by a 5-kg infant at 500 g/day would provide a daily Dieldrin intake of approximately 0.75 μg/kg, or 7.5 times the FAO/WHO ADI.

The general concentrations of organochlorine insecticides in Illinois milk in 1971-1973 are shown in Table VI-15 (Moore, 1975).

TABLE VI-15

Organochlorine Insecticides
Concentration in Illinois Milk, ppm

Insecticide	1971	1972	1973	Average
Chlordane	0.02	0.04	0.06	0.05
DDT	0.05	0.02	0.01	0.03
Dieldrin	0.08	0.04	0.08	0.07
Heptachlor	0.03	0.03	0.05	0.05
Lindane	T*	0.02	0.01	0.02

*T = trace.

Of 200 samples analysed, 87% were positive for Chlordane, 92% for DDT, 94% for Dieldrin, 93% for Heptachlor, and 81% for Lindane (Moore, 1975).

Food chain effects. The cyclodiene insecticides--especially the epoxides Dieldrin, Heptachlor epoxide, and Oxychlordane--are very stable, both environmentally and biologically, and have high lipid-water partition coefficients. Thus, they pass through food chains and undergo biologic magnification (Lu *et al*., 1975; Metcalf *et al*., 1973).

These factors account for the bioaccumulation of these persistent products in human adipose tissue. The values shown in Table VI-16 indicate the average amounts found in fiscal 1970-1974 in over 1,400 bioassays of U.S. human fatty tissues (NAS, 1975).

TABLE VI-16: Pesticides in Fatty Tissue

Insecticide	Concentration, ppm 1970	1971	1972	1973	1974
Dieldrin	0.27	0.29	0.24	0.24	0.20
Heptachlor epoxide	0.17	0.12	0.12	0.12	0.10
Oxychlordane	--	--	0.15	0.15	0.15
DDT-T	11.65	11.55	9.91	8.91	7.83

The presence of Oxychlordane was first discovered in 1972. The decreasing amounts of DDT-T clearly reflect the banning of this compound.

The human is at the top of the food pyramid; thus, persistent pesticide residues, such as those of the cyclodienes, are excreted in human milk; see Table VI-17 (Curley and Kimbrough, 1969). Recent unpublished studies have also identified oxychlordane.

TABLE VI-17: Pesticides in Human Milk

	Concentration, ppm	
Insecticide	mean	range
Dieldrin	0.0073	0.0029-0.0146
Heptachlor epoxide	0.0027	<0.0001-0.0044
DDT-T	0.0027	0.0404-0.1563

Dieldrin provides a graphic example of the propensity to persist in food chains and to accumulate in lipid tissues. Gannon *et al.* (1959) demonstrated that Dieldrin fed to chickens was stored in body fat to very much higher concentrations than when fed to steers, hogs, and lambs. For example, Dieldrin fed at 0.1 ppm was stored at 4.1 ppm, and that fed at 0.75 ppm was stored at 35.7 ppm. However, it was not until 1974 that it was demonstrated that as many as 20 million chickens in Mississippi fed on waste food stocks of soybean oil that had been processed on soybeans grown in Aldrin-treated soil containing illegal residues of Dieldrin (generally at 0.01-0.04 ppm) contained Dieldrin residues in their body fat greatly exceeding the FDA "safe limit" of 0.3 ppm and ranging up to 30 ppm (Moore, 1975). The chickens had to be destroyed as unfit for human consumption (Pesticide Chem. News, 1974).

II. METABOLISM

The breakdown pathways of the cyclodienes are relatively complex (Brooks, 1973) and are still in the process of elucidation. Many of the degradation products are highly active neurotoxins--e.g., photodieldrin--and present a substantial degree of environmental hazard. The metabolic pathways can only be summarized here.

Aldrin and dieldrin. The dominant reaction of Aldrin is epoxidation at the double bond to form the 6,7-epoxide dieldrin. This is a microsomal oxidation and occurs photochemically and biologically in soils, plant tissues, and in all animals studied (Gannon and Decker 1958). Thus the very stable Dieldrin appears everywhere in the environment as the major contaminant following the use of Aldrin. Further biological or photochemical reaction of Dieldrin produces photodieldrin or 10-oxa-1,6-exo-4,5,11,11-hexachloro-(6.3.1.1^{3,8}.1^{9,11}.0^{2,7}.0^{5,12})tridecane a cage-like compound (Matsumura *et al.*, 1970). Photodieldrin is about 5 times more acutely toxic to laboratory animals than Dieldrin. Aldrin is also degraded in plants and animals to hexachloro-hexahydro-1,4-*endo*-methyl-eneindene-5, 7-dicarboxylic acid (Klein *et al.*, 1973) and to aldrin-*trans*-diol. In animals 9-hydroxydieldrin, 9-keto-dieldrin, and keto-photodieldrin are also formed as excretory metabolites (Mathews *et al.*, 1971). The hydroxy degradation products are largely conjugated in animals before excretion.

Endrin. This cyclodiene exists in the *endo-endo* configuration, which is inherently less stable than the *endo-exo* configuration of its stereoisomer dieldrin. Endrin isomerizes in light, to form Δ-ketoendrin, or 1,8-*exo*-9,10,11,11-hexachloropentacyclo (6.2.1.1^{3,6}, ^{2,7},0^{4,10})-dodecan-5-one. In animals, Endrin is degraded, largely to 9-ketoendrin and 9-hydroxyendrin, but also to 5-hydroxyendrin (Baldwin *et al*., 1970).

Heptachlor and Heptachlor epoxide. Heptachlor is rapidly oxidized to the 2,3-heptachlor epoxide (Davidow and Radomski, 1953). This is a microsomal oxidation and occurs both photochemically and biologically in soils, plant tissues, and all animals studied (Gannon and Decker, 1958). Thus, the stable heptachlor epoxide appears everywhere in the environment as the major contaminant after the use of Heptachlor. Heptachlor epoxide is more toxic to animals than heptachlor. Heptachlor differs from Aldrin, in that it is much more easily hydrolysed, because of the allylic C=C-CHCl structure, to form 1-hydroxychlordene or 1-hydroxy-4,5,6,7,8,8-hexachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene, which is converted to the 2,3-epoxide, an excretory metabolite in animals (Lu *et al*., 1975). Heptachlor forms a photoproduct, photoheptachlor. Heptachlor epoxide forms photoheptachlor epoxide and slowly hydrolyses to the diol (Menzie, 1974).

Chlordane. Both the *cis*- and *trans*- Chlordanes form a single epoxide, Oxychlordane, or 1-*exo*-2-*endo*-4,5,6,7,8,8-octachloro-2,3-*exo*epoxy-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene (Schwemmer *et al*., 1970). This has only recently been recognized as the major terminal residue in animal tissues and milk after ingestion of Chlordane (Barnett and Dorough, 1974). Oxychlordane is more toxic to animals than either of the Chlordane isomers. There is also evidence of the formation of hydrophilic degradation products, such as chlordanedihydrodiol and 1-hydroxy-2-chlorodihydrochlordene (Korte, 1967). Other degradation products identified include 1-hydroxychlordane and photochlordane, a cage-like compound (Menzie, 1974).

III. HEALTH ASPECTS

The effects of the cyclodienes on animal and human health are very subtle and complex. These are the most hazardous of all pesticides, because of their persistence, fat storage, and central nervous system target site. Their effects can be reviewed only briefly here.

A. Observations in Man

Human illness and death have been observed after poisoning during the manufacture, spraying, or accidental ingestion of the cyclodienes. Typical symptoms of poisoning result from stimulation of the central nervous system and include headache, blurred vision, dizziness, slight involuntary muscular movements, sweating, insomnia, bad dreams, nausea, and general malaise. More severe illness is characterized by jerking of muscles or groups of muscles and epileptiform convulsions, with loss of consciousness, involuntary incontinence of urine and feces, disorientation, personality changes, psychic disturbances, and loss of memory. Such seizures may recur for 2 - 4 months after cessation of exposure and are marked by abnormal encephalographic patterns. These symptoms of severe poisoning have developed in 10 - 20% of spraymen working in WHO house-spraying programs (Hayes, 1957, 1959), and such poisoning has not been eliminated in any spray program.

Epidemics of Endrin poisoning have occurred after the eating of bread made from flour accidentally contaminated with Endrin; there were 59 illnesses in one episode (Davies and Lewis, 1956) and 874, with 26 deaths, in Saudi Arabia (Weeks, 1967). At least 97 cases of fatal Endrin poisoning were recorded through 1965 (USEPA, 1973a). It appears that ingestion of Endrin at 0.2 - 0.25 mg/kg can produce convulsions in humans (Hayes, 1963).

Workers in a plant manufacturing and formulating Aldrin, Dieldrin, Isodrin, and Endrin had epileptiform convulsions (3.1%) and had encephalograms suggesting brain stem injury (20.5%). The encephalograms usually returned to normal within 1 - 6 months after exposure ceased (Hoogendam et al., 1962).

B. Observations in Other Species

Acute Effects. The acute dermal and oral LD_{50} values of the various cyclodienes and key degradation products in rats, as measured under uniform conditions, were given by Hayes (1963) and are summarized in Table VI-18.

TABLE VI-18. LD_{50}'s of Cyclodienes

Substance	Oral LD_{50}, mg/kg		Dermal LD_{50}, mg/kg	
	Male	Female	Male	Female
Aldrin	39	60	98	98
Dieldrin	46	46	90	60
Photodieldrin	9.6			
Endrin	17.8	7.5	-	15
Chlordane	335	430	840	690
Heptachlor	100	162	195	250
Heptachlor epoxide	46.5	61.3	-	-
Endosulfan	43	18	130	74

Not only are such compounds as Endrin extraordinarily toxic (it is registered as a rodenticide), but the dermal toxicity is roughly equivalent to the oral toxicity.

Chronic Effects. The results of chronic feeding of the cyclodienes to laboratory animals are extraordinarily severe, and true no-adverse-effect dosages have never been determined for some of the compounds, such as Dieldrin, Heptachlor, and Chlordane (Walker *et al.*, 1972). Toxicological evaluation is complicated by the *in vivo* conversion of the cyclodienes to epoxides by microsomal oxidation: Aldrin to Dieldrin, Heptachlor to Heptachlor epoxide (Davidow and Radomski, 1953) and Chlordane isomers to Oxychlordane (Schwemmer *et al.*, 1970). Dieldrin, Heptachlor epoxide, and Oxychlordane are very persistent and fat soluble and are the dominant metabolites stored in human and animal tissues and excreted in milk. The amounts of these cyclodienes found in human adipose tissues in 1970-1974 were: Dieldrin 0.00-15.2 ppm (mean, 0.18 ppm); Heptachlor epoxide, 0.00-10.62 ppm (mean, 0.17 ppm); and Oxychlordane (mean, 0.15 ppm) (NAS, 1975).

Chlordane fed to rats at 2.5 ppm caused slight liver damage (Lehman, 1952). Heptachlor fed to rats at 0.1-1.0 ppm resulted in the accumulation of Heptachlor epoxide in the body fat. When it was fed to dogs at 1 mg/kg/day, three of four animals died in 265-424 days; at 5 mg/kg/day, death occurred in 21 - 22 days (Lehman, 1952). Aldrin fed to rats at 5 ppm produced no adverse effects; fed to dogs at 1 mg/kg/day, it caused death in 21 - 22 days (Lehman, 1952).

Dieldrin fed to rats at 5 ppm produced no adverse effect. When it was fed to dogs at 0.5 mg/kg/day, two of four animals died, in 14 and 201 days; 1 mg/kg/day, both animals tested died, in 83 and 300 days; at 2 mg/kg/day; both animals died, in 22 and 35 days (Lehman, 1952). In recent studies, Dieldrin fed to mice at 2.5 and 5 ppm in the diet shortened the life span; at 0.1-1.0 ppm, it caused a progressive increase in malignant hepatomas (Walker *et al.*, 1972). Thus, the no-adverse-effect dosage has never been determined.

Endrin fed to rats at 1 and 5 ppm in the diet produced no obvious effects over the life span, except for liver enlargement at 5 ppm. When it was fed at 25 ppm, the life span was shortened, and diffuse degeneration was seen in brain, liver, kidneys, and adrenals. Mice fed Endrin at 0.1 - 6.0 ppm over their life span showed increased liver weights at 2 and 4 ppm and vascular damage of liver cells. Convulsions were observed in dogs fed 2 and 4 ppm, and autopsies revealed pathologic changes in the brain (USEPA, 1973a).

Aldrin, Dieldrin, and Endrin at very low dosages affect the central nervous system, producing encephalographic changes and altering behavior. Medved *et al.* (1964) found that rats fed Aldrin at 1 mg/kg/day or made to inhale 0.1 µg/liter of air had marked lowering of conditioned reflexes and of unconditioned food and orientation reflexes, which required up to 8 days to return to normal. Sheep fed Dieldrin at 0.5 and 2.5 mg/kg/day had abnormal encephalographic and behavioral responses (Sandler *et al.*, 1968, Van Gelder *et al.*, 1969).

Mutagenicity. Dieldrin was not mutagenic in the *Salmonella*/microsome test (McCann, 1975). There is no available information on Aldrin, Endrin, Chlordane, Heptachlor and Heptachlor epoxide.

Carcinogenicity. The Mrak Commission (Mrak, 1969) judged Aldrin, Dieldrin, and Heptachlor as positive for tumor induction in one or more species of laboratory test animals. Dieldrin fed to mice (CF1) for 2 years (Walker *et al.*, 1972) produced a dosage-dependent incidence of hepatomas. In males, the incidences were: controls, 7%, on 0.1-ppm Dieldrin, 21%; on 1-ppm Dieldrin, 28%; and on 10-ppm Dieldrin, 53%. In females, the incidences were: controls, 4%; on 0.1-ppm Dieldrin, 30%; on 1-ppm Dieldrin, 42%; and on 10-ppm Dieldrin 62%. Although the malignant nature of these tumors was questioned by the experimenters, they were later declared as true metastatic malignancies by a panel of experts (USEPA, 1974d). Experiments with rats and dogs were less definitive (Walker *et al.*, 1969). An additional 2-year feeding study with Dieldrin and Photodieldrin has been reported by Walton *et al.* (1971).

Heptachlor epoxide fed to rats (CFN) over a 2-year period at 0.5, 2.5, 5.0, 7.5, and 10 ppm in the diet produced increased numbers of tumors, mostly adrenal, in all groups, compared with controls. Even at 0.5 ppm, there was a 62.5% incidence of tumors in male rats, compared with 34.78% in controls, and 82.61% incidence in female rats, compared with 58.17% in controls. From these apparently unpublished results, Heptachlor epoxide was judged as a highly potent carcinogen (Kettering Laboratory, 1959).

Chlordane and Heptachlor were evaluated for carcinogenicity by the National Cancer Institute and were found to be carcinogenic in mice (B6C3F1), with a high incidence of hepatocellular carcinomas when fed over an 80-week period, and in rats, in which hepatic nodules and liver hyperplasia were produced. Chlordane fed at 56 ppm produced 88.9% hepatocellular carcinoma in male mice, compared with 10% in controls, and fed at 64 ppm produced 69.6% hepatocellular carcinoma in female mice, compared with 0% in controls. Heptachlor fed at 13.8 ppm produced 70.2% hepatocellular carcinoma in male mice, compared with 11.1% in controls, and fed at 18.0 ppm produced 69.0% hepatocellular carcinoma in female mice, compared with 10% in controls. It was judged that both Chlordane and Heptachlor are potent liver carcinogens in both sexes of mice, although the results have apparently not yet been published (NCI, 1975).

Endrin was fed to rats at 2, 6, or 12 ppm in the diet for 2 years without producing primary malignant hepatic tumors or increasing tumor incidence in any organs (Dieckmann et al., 1970).

Davis and Fitzhugh (1962) fed Aldrin at 10 ppm in the diet to C_3HeB/Fe mice for two years. There was a statistically significant increase in the number of benign liver tumors in the Aldrin-fed mice as compared to controls. This study is cited by the Mrak Commission (Mrak, 1969) to be positive evidence for tumor induction for this compound.

Aldrin fed to rats at 2.5, 12.5 and 25 ppm in the diet for 2 years produced non-dosage-dependent tumors which were not significantly different from the tumor incidence in the controls. (Cleveland, 1966.)

Reproduction. Endrin fed to mice at 5 ppm for 30 days produced significantly smaller litters than in controls. However, 7 ppm had no significant effect on mean litter size and litter production frequency when fed to Saskatchewan deer mice (Peromyscus maniculatus) over intermittent periods. Rats fed 2.0 ppm over three generations had no observable effect in fertility, gestation, viability, and lactation (cited in USEPA, 1973a).

When quail were fed 1 ppm, no eggs were produced during the reproductive period. Endrin fed at 10 ppm reduced egg production in pheasants and reduced survival of the chicks (Cited in USEPA, 1973a).

Evidence presented at EPA hearings (1974d) indicated substantial effects of Dieldrin on animal reproduction. For example, raccoons fed Dieldrin at 2 and 6 ppm in the diet produced 20.0 and 20.2%, respectively, as many young as did untreated controls. Litter size was also reduced. In further study, raccoons fed Dieldrin at 2 ppm had abnormal estrous cycle, reduced ovulation rate, reduction of pregnancy to 25-30% of that in controls, increased resorption of embryos, and reduction in litter size. Dieldrin also influenced spermatogenesis, sperm quality, and fertility adversely in male raccoons.

Teratogenicity. Aldrin, Dieldrin and Endrine were studied by Ottolenghi et al. (1974) in hamsters and mice. Single oral doses of approximately one-half the respective LD$_{50}$ doses were given on days 7, 8 or 9 of gestation in the hamster and on day 9 of gestation in the mouse. A significant number of defects were produced in both species.

Chlordane was found not to be teratogenic in rats at 120 to 300 ppm in diet (Ingle, 1952).

IV. Carcinogenic Risk Estimates.

Dieldrin, Chlordane and Heptachlor have produced dose-related hepatomas when fed to mice (Walker et al., 1972 and NCI, 1975). For each compound the available sets of dose-response data were individually considered as described in the risk section in the margin-of-safety chapter. Each set of dose-response data was used to statistically estimate both the lifetime risk and an upper 95% confidence bound on the lifetime risk at the low-dose level. These estimates are of lifetime human risks and have been corrected for species conversion on a dose-per-surface-area basis. The risk estimates are expressed as a probability of cancer after a lifetime consumption of 1 liter of water per day containing Q ppb of the compound of interest. For example a risk of 1X10^{-6} Q implies a lifetime probability of 2X10^{-5} of cancer if 2 liters/day were consumed and the concentration of the carcinogen was 10 ppb (i.e. Q=10). This means that at a concentration of 10 ppb during a lifetime of exposure this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the U.S. is taken to be 220 million people, this translates into 4400 excess lifetime deaths from cancer or 62.8 per year. Since several data sets are typically available the range of the dose risk estimates are reported.

For Dieldrin at a concentration of 1 µg/liter (Q=1) the estimated risk for man would fall between 0.8-1.5X10^{-4} Q. The upper 95% confidence estimate of risk at the same concentration would be between 1.9-2.6X10^{-4} Q.

For Chlordane at a concentration of 1 µg/liter (Q=1) the upper 95% confidence estimated of risk for man would be between 0.96-1.8X10^{-4} Q.

For Heptachlor at a concentration of 1 µg/liter (Q=1) the upper 95% confidence estimate of risk for man would be from 3.5 to 4.8X10^{-4}Q.

V. CONCLUSIONS AND RECOMMENDATIONS

The cyclodiene insecticides--particularly the persistent epoxides, Dieldrin, Endrin, Heptachlor epoxide, and Oxychlordane--present the greatest hazards of all residual pesticides in water. At low dosages, they are highly active hepatocarcinogens and have a dangerous effect on the central nervous system of man and higher animals, leading to apparently irreversible changes in encephalographic and behavioral patterns. They are highly persistent biologically and can accumulate in animal fats and exist in milk.

In light of the above and taking into account the carcinogenic risk projections it is suggested that very strict criteria be applied when limits for Dieldrin, Heptachlor and Chlordane in drinking water are established. Before limits for Aldrin, Endrin and Heptachlor epoxide in drinking water can be established, more toxicological data must be gathered and evaluated. The available chronic-toxicity data are summarized in Tables VI-19, 20, 21, and 22.

TABLE VI-18: Summary of Chronic Toxicity Data I: Aldrin and Dieldrin

Species	Duration of Study	Dosage Levels and No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Dieldrin					
mouse	132 weeks	0.0 ppm 288M 297F 0.1 ppm 124M 90F 1.0 ppm 111M 89F 10.0 ppm 176M 148F	≤ ≤0.1 ppm	liver tumours M6.9% F 4.5% M21% F30% M36% F42.5% M51.4% F62.3%	Walker et al., 1973
rat (CFE)	2 years	0.0 ppm 13M 23F 0.1 ppm 23M 23F 1.0 ppm 23M 23F 10.0 ppm 23M 23F	≤0.1 ppm	renal liver tumours M28% F65% M26% F65% M32% F61% M35% F52%	Walker et al., 1969
dogs (beagle)	2 years	0.00 ppm 5M 5F 0.005 mg/kg/d 5M 5F 0.5 mg/kg/d 5M 5F	≤0.1 ppm	ratios increased liver weight M3.37% F3.32% M3.61% F3.56% M4.28% F4.51%	Walker et al., 1969

[This compound is an animal carcinogen]

Species	Duration of Study	Dosage Levels and No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Aldrin					
Rat	2 years	0 [illegible]M [illegible]F 2.5 29M 32F 12.5 27M 36F 25.0 26M 33F	≤2.5 ppm	Tumours M7.69% F11.32% M3.45% F 3.13% M0 F 8.33% M3.84% F 3.03%	Cleveland, 1966
Mice	2 years	107M 107F 10 ppm	10 ppm	Hepatic cell adenoma	Davis and Fitzhugh, 1962

[This compound is an animal carcinogen]

TABLE VI-20: Summary of Chronic Toxicity Data for Endrin

Species	Duration of Study	Dosage Levels	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Rat	2 years	0			Deichmann et al. 1970
		2 ppm		"no primary malignant tumors"	
		6 ppm		"no primary malignant tumors"	
		12 ppm		"no primary malignant tumors"	
Dog (Beagle)	19 months	0			
		1 ppm		increased liver/body ratio	Cited in EPA, 1973
		3 ppm		increased liver/body ratio	
Dog	2 years	0			
	(7 M, & 7 F at each level)	0.1 ppm			Cited in EPA, 1973
		0.5 ppm	0.5 ppm		
		1.0 ppm			
		2.0 ppm		convulsions, increased/liver body ratio, cell degeneration	
		4.0 ppm		convulsions, increased/liver body ratio, cell degeneration	

This compound is a suspected animal carcinogen.

TABLE VI-21. Summary of Chronic Toxicity Data for Chlordane

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse-effect Level or Lowest Minimal-effect Level	Effect Measured	Reference
Mice ($B6C3F_1$)	90 wks	0 ppm M 48 F 48 30 ppm 56 ppm 64 ppm	≤ 30 ppm	liver tumors (carcinoma) M 20% F 0% M 33% F 6.2% F 88.9% *F 73.9%	National Cancer Inst., 1975
Rat (OM)	110 wks	0 ppm M 7 F 10 121 ppm F 49 203 ppm M 43 241 ppm F 43 407 ppm M 42	≤ 120 ppm	liver* tumors (carcinoma) M 0% F 0% F 2.0% F 2.0% F 2.3% F 4.7% F 0.0%	National Cancer Inst., 1975

*Liver hyperplasia: M, 0% controls, low dose 3.0%, high dose 14.3%, F, controls 0, low dose 14.7%, high dose 40.9%.

[This compound is an animal carcinogen.]

TABLE VI-22. Summary of Chronic Toxicity Data for Heptachlor and Heptachlor Epoxide

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse-effect Level or Lowest-Minimal effect Level	Effect measured	Reference
Heptachlor					
Mouse (B6C3F1)	90 wks	0 ppm M 58 F 60	≤6.1 ppm	liver tumors (carcinoma) M 11.1% F 10%	National Cancer Inst., 1975
		6.1 ppm M 49		M 28.6%	
		9.0 ppm F 46		F 10.4%	
		13.8 ppm M 47		M 80.0%	
		18.0 ppm F 42		F 69.0%	
Rat (OM)	110 wks	0 ppm M 10 F 10	≤18.9 ppm	liver tumors (carcinoma) M 0 F 0	National Cancer Inst., 1975
		18.9 ppm F 48		F 12.5%	
		38.9 ppm M 43		M 2.3%	
		37.8 ppm F 47		F 8.5%	
		77.9 ppm M 45		M 11.1%	

[This compound is an animal carcinogen.]

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse-effect Level or Lowest-Minimal effect Level	Effect measured	Reference
Heptachlor Epoxide					
Rat (CFN)	2 yrs	0 ppm M 23 F 24	≤0.5 ppm	endocrine tumors M 35% F 54%	Kettering Laboratory, 1959
		0.5 ppm M 24 F 23		M 62.5% F 82.6%	
		2.5 ppm M 20 F 25		M 60% F 79.2%	
		5.0 ppm M 20 F 22		M 60% F 77%	
		7.5 ppm M 24 F 22		M 54% F 90.9 %	
		10.0 ppm M 23 F 23		M 56% F 73.9%	

[This compound is a suspected animal carcinogen.]

DDT and DDE

I. INTRODUCTION

DDT, or 2,2-*bis*-(*p*-chlorophenyl)-1,1,1-trichloroethane, was patented as an insecticide in 1939 by Swiss chemist Paul Muller. After a period of extensive use for the control of malaria, typhus, and other insect-transmitted diseases during World War II, it became the prototype of the synthetic insecticides. At the height of its use in the United States, in 1963, production was 176 million pounds, and DDT was registered for use on 334 agricultural commodities. DDT has been used very extensively all over the world, both in malaria control and in agriculture, and it is estimated that more than 4.4 billion pounds has been used for insect control since 1940, about 80% in agriculture. Because of the extensive environmental problems resulting from its stability and high lipid-water partitioning, DDT was banned for all but essential public-health use in the United States on January 1, 1973.

DDT is produced by condensing chlorobenzene with chloral. The technical product contains about 80-90% *p,p*'-isomer. DDT is soluble in water at 0.0012 ppm at 25°C.

The persistence of DDT, DDE (or 2,2-*bis*-(*p*-chlorophenyl)-1,1-dichloroethylene), and DDD (or 2,2-(*p*-chlorophenyl)-1,1-dichloroethane) has made them ubiquitous contaminants of water. The total residues are commonly referred to as "DDT-T". In an extensive 1958-1965 survey of the rivers of the United States, Breidenbach *et al.* (1967) found DDT in every river surveyed at 0.008-0.144 ppb; DDE at 0.002-0.011 ppb, and DDD at 0.004-0.080 ppb. The highest concentrations were generally found in the West and South, where 44% of the samples were positive for DDT and 39% for DDE. More than 500 grab samples of finished drinking water and related raw water from the Mississippi and Missouri Rivers were analyzed by Schafer *et al.* (1969); more than 33% of the finished-water samples contained DDT-T.

An EPA study of over 700 water utilities serving airplane, train, and bus terminals showed DDT in six of 106 samples at 1-2 ppt and in five of 83 samples of finished water at 6-68 ppt (USEPA, 1975j).

In Iowa, Richard *et al.* (1975), assayed DDE in various surface, subsurface, and finished waters. Water from the South Skunk River near Ames contained DDE at 3 - 1,820 ppt, with the highest concentrations in June 1974. Similar results were found in Indian Creek (2 - 3,920 ppt), and in a drainage ditch near Fernald, Iowa (4 - 1,150 ppt). Surface water had DDE at 1 - 248 ppt (average, 66 ppt) in the Des Moines River, 2 - 250 ppt (average 59 ppt) in the Raccoon River, 0 - 350 ppt (average, 212 ppt) in the Red Rock Reservoir, and 5 - 1,121 ppt (average, 420 ppt) in the Rathbun Reservoir. Other surface-water values found were: Cedar River, 480 ppt; Iowa River, 350 ppt; Des Moines River, 70 ppt; and Mississippi River (near McGregor Iowa), 2 ppt. The Mississippi at New Orleans had DDE at 40 ppt. Finished water at Cedar Rapids contained DDE at 20 ppt, but other finished water had less than 0.5 ppt.

Lake Michigan contains DDT-T at an average of 6 ppt. Most fishes from Lake Michigan contain DDT residues in excess of the 7 ppm FDA "safe limit" and the overall biomagnification from water to fish may exceed a factor of 3 x 10^5.

Water standards have been proposed for DDT in finished water (Schafer et al., 1969). The DDT-T concentration suggested in 1965-1966 and based on maximal acceptable concentrations of the Subcommittee on Toxicology was 42 ppb. This was drastically lowered to 2.5 ppb, by Ettinger and Mount (1969), on the basis of a maximal reasonable stream allowance.

DDT and its breakdown products are ubiquitous and, because of biomagnification and persistence, are in virtually every food product. "Market-basket" surveys of the U.S. diet, collected in five major U. S. cities and designed to represent the diet of a 16 to 19-year-old male, show the intakes in Table VI-23 (NAS, 1975).

TABLE VI-23. Pesticides in Diet

Daily Dietary Intake, in mg

Pesticide	1965	1966	1967	1968	1969	1970	6-Year Average
DDT	0.031	0.041	0.026	0.019	0.016	0.015	0.025
DDE	0.018	0.028	0.017	0.015	0.011	0.010	0.017
DDD	0.013	0.018	0.013	0.011	0.005	0.004	0.011
DDT-T	0.062	0.087	0.056	0.045	0.032	0.029	0.053

Calculated as human intake in mg/kg/day, the combined DDT-T was about 0.2 that of the FAO/WHO Acceptable Daily Intake of 0.005 mg/kg/day. The dietary intake was 0.0009 mg/kg/day in 1965, 0.0010 in 1966, 0.0008 in 1967, and 0.0007 in 1968 (Mrak, 1969).

DDT in milk. DDT is present in milk, everywhere. Moore (1975) surveyed Illinois milk in 1971-1973 and found DDT at 0.05 ppm in 1971, 0.02 ppm in 1972, and 0.03 ppm in 1973. The human is at the top of the food pyramid, so human milk is especially contaminated. Curley and Kimbrough (1969) found DDT-T residues averaging 0.0784 ppm in U.S. samples (range, 0.0404-0.1563 ppm).

II. METABOLISM AND DEGRADATION

Although DDT is highly stable and persistent, it does undergo a relatively complex series of degradative changes, both biologically and environmentally. The dominant reaction is dehydrochlorination to form DDE, which is much less toxic to insects and higher animals, but has about the same solubility in water (0.0013 ppm) and high lipid-water partitioning. DDE is almost nondegradable, both biologically and environmentally. Thus, DDE is the predominant residue stored in tissues, increasing in relative concentration for each trophic level (Woodwell *et al.*, 1967) and reaching about 70% of DDT-T in humans (Durham 1969). Nothing is certain about the degradation pathway of DDE.

DDT is also reductively dechlorinated in biologic systems to form DDD. DDD is less stable than DDT or DDE and is the first step on the degradation pathway in animals (Morgan and Roan, 1974) and in the environment (Metcalf, 1973). DDD is dehydrochlorinated to DDMU, or 2,2-*bis*-(*p*-chlorophenyl)-1-chloroethylene; reduced to DDMS, or 2,2-*bis*-(*p*-chlorophenyl)-1-chloroethane; dehydrochlorinated to DDNU, or 2,2-*bis*-(*p*-chlorophenyl)-ethylene; reduced to 1,1-*bis*-(*p*-chlorophenyl)-ethane; and eventually oxidized to DDA or bis-(p-chlorophenyl)-acetic acid. This compound is much more soluble in water than DDT and is the ultimate excretory product of DDT ingestion and storage in higher animals and humans. Environmentally, DDT residues are converted to *p,p*'- dichlorobenzophenone.

DDT is also degraded to a slight extent by microsomal oxidase enzymes by attack at the α-H to form dicofol, or 1,1-*bis*-(*p*-chlorophenyl)-2,2,2-trichloroethanol. Very recently, a new anaerobic degradation pathway, found especially in sewage sludge, was discovered in the conversion by bacteria to form DDCN, or *bis*-(*p*-chlorophenyl)-acetonitrile (Metcalf, 1973).

The kinetics of storage and loss of DDT and DDE in humans has been investigated intensively (Durham, 1969; Morgan and Roan, 1974). In humans, DDT is stored in fat at about 10 times the concentration of intake. The average U.S. inhabitant in 1968 had DDT-T stored in his fat at 10 ppm; about 70% of this was DDE. Storage can reach very high values; e.g., a DDT formulator stored DDT-T at 1,131 ppm, 43% of it as DDE (Durham, 1969). Conversion of DDT to DDE in the human body is very slow, i.e., less than 20% over 3 years. DDT is eliminated from the human body through first-order reduction to DDD and conversion to the more water-soluble DDA, with a biologic half-life of about 1 year. DDE is eliminated much more slowly, with a biologic half-life of about 8 years. Its pathway of elimination is unknown; it may be slowly excreted as DDE (Morgan and Roan, 1974).

III. HEALTH ASPECTS

A. Observations in Man

There are no definite examples of human fatality due to ingestion of DDT, but a dosage of 10 mg/kg has produced illness in some (but not all) subjects, without convulsions. Convulsions have frequently occurred at 16 mg/kg or higher. Human volunteers have consumed 35 mg/day (about 0.5 mg/kg/day) for as long as 25 months without ill effects (Hayes, 1963). These subjects stored 101 - 466 ppm in their body fat after 12 months and 105 - 659 ppm after 21 months.

DDT-T concentrations found in human fat over FY 1970-1974, in over 1,400 bioassays of U.S. human tissues, were 11.65, 11.5, 9.91, 8.91, and 7.83 ppm in fiscal 1970, 1971, 1972, 1973, and 1974, respectively (NAS, 1975).

The decline undoubtedly represents the effects of decreased use and the banning of DDT in 1973.

B. Observations in Other Species

Acute Effects. The oral LD_{50} of DDT in rats is 113 mg/kg in males and 118 mg/kg in females. The dermal LD_{50} in female rats is 2,510 mg/kg (Hayes, 1963). DDE has an oral LD_{50} in rats of 880 mg/kg in males and 1,240 mg/kg in females. DDA has an oral LD_{50} in rats of 740 mg/kg in males and 600 mg/kg in females.
The oral LD_{50} of DDT in dogs is 60-75 mg/kg, in rabbits is 250-400 mg/kg, and in mice is 200 mg/kg (Pimentel, 1971).

Chronic Effects. When rats were fed DDT at 5-10 ppm over the lifetime, microscopic alterations were reported in liver cells, including centrilobular enlargement with increased oxyphilia and peripheral margination of the basophilic granules. These effects became moderate when DDT was fed at 50 ppm and were pronounced at 400 ppm; however, 50 ppm was tolerated without gross toxicity, and 100 ppm with only slight symptoms of poisoning (Lehman, 1952a). The high lipid-water partition results in pronounced fat storage; when DDT was fed at 1 ppm to rats for 15 weeks, it was stored in fat at 13 ppm in males and 18 ppm in females, and the corresponding values for 50 ppm were 284 and 588 ppm (Lang *et al.*, 1950). It has been estimated that fat storage occurs at about 20 times the dietary intake.

Mice fed DDT at 100 ppm in the diet had a considerably shortened life span, although this was not apparent at 50 ppm (Walker *et al.*, 1972).

Dogs tolerated daily DDT intakes of 10 mg/kg in corn oil for three years without gross effects, but died after a few months at 50 and 80 mg/kg (Lehman, 1952b).

Mutagenicity. DDT was not mutagenic in the *Salmonella*/microsome test (McCann *et al.*, 1975).

Carcinogenicity. The Mrak Commission (1969) judged DDT to be positive for tumor induction in one or more s [illegible] of test animals. This, with its high persistence and [illegible] of fat storage, has caused substantial environmental concern. Tarjan and Kemeny (1969) showed a generalized increase in frequency of tumors in five generations of mice after feeding DDT at 3 ppm, and Faur and Kemen (1969) found increased numbers of malignancies when DDT was fed to mice at 0.3 - 0.6 mg/kg of body weight. The WHO has repeated these studies and found that DDT fed to mice at 0.3 mg/kg/day over a lifetime produced a significant increase in liver tumors in males (WHO, 1973).

Teratogenicity. Although the thickness of egg shells of birds was reduced by DDT (Hickey and Anderson, 1968), no teratogenic effects have been identified in chicks, mice (Ware and Good, 1967) or in rats (Ottoboni, 1969).

IV. CARCINOGENIC RISK ESTIMATES

Despite the positive results in mice, oral administration of DDT to rats has not provided convincing evidence of carcinogenicity. Feeding studies on dogs and monkeys have also not shown DDT to be carcenogenic, but these studies are of limited value due to small group size and short duration.

Studies on human workers occupationally exposed to DDT have not shown an increased incidence of cancer, but these studies are limited by time factors. Terminal cancer patients have been observed to have higher fat concentrations of DDT, but a causal relationship is difficult to prove (IARC, 1974).

Only the data from feeding studies in mice can be statistically treated to provide an estimate of risk for man. Several species of mice have developed hepatomas after oral exposure to DDT.

The available sets of dose response data were individually considered as described in the risk section in the margin-of-safety-chapter. Each set of dose-response data was used to statistically estimate both the lifetime risk and an upper 95% confidence bound on the lifetime risk at the low dose level. These estimates are of lifetime human risks and have been corrected for species conversion on a dose-per-surface-area basis. The risk estimates are expressed as a probability of cancer after a lifetime consumption of 1 liter of water/day containing Q ppb of the compound of interest. For example, a risk of 1×10^{-6} Q implies a lifetime probability of 2×10^{-5} of cancer if 2 liters per day were consumed and the concentration of the carcinogen was 10 ppb (i.e. Q=10). This means that at a concentration of 10 ppb during a lifetime of exposure this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the U.S. is taken to be 220 million people this translates into 4400 excess lifetime deaths from cancer or 62.8 per year. Since several data sets are typically available the range of the low dose risk estimates are reported.

For DDT at a concentration of 1 µg/liter (Q=1) there are several risk estimates depending on which feeding study is evaluated. Four studies (Innes et al., 1969; Tomatis et al., 1972; Walker et al., 1972; and Thorpe and Walker, 1973) provide a risk to man of from $0.18-13.0 \times 10^{-6}$ Q. The upper 95% confidence estimate of risk at the same concentration is from $0.65-20.0 \times 10^{-6}$ Q.

V. Conclusions and Recommendations

DDT is of moderate acute toxicity to man and most other organisms. However, its extremely low solubility in water (0.0012 ppm) and high solubility in fat (100,000 ppm) result in great bioconcentration. Its principal breakdown, product, DDE, has very similar properties. Both compounds are also highly persistent in living organisms, so the major concern about DDT toxicity is related to its chronic effects, which are summarized in Table VI-24.

In light of the above and taking into account the carcinogenic risk projections it is suggested that very strict criteria be applied when limits for DDT and DDE in drinking water are established.

TABLE VI-24. Summary of Chronic Toxicity Data for DDT and DDE

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse-effect Level or Lowest Minimal-effect Level	Effect measured	Reference
Mouse	5 generation	0 (406 animals)		2.23% tumors 1.23% leukemia	Tarjan and Kemeny, 1969
		3 ppm (684 animals)	3 ppm	28.4% tumors 11.57% leukemia	
		0.3-0.6 mg/kg/d	≤0.3 mg/kg/day	tumors	Faur and Kemeny 1969
		0.3 mg/kg/d	≤0.3 mg/kg/day	liver tumors	WHO, 1973
Rat	2 years	5 ppm	≤ 5 ppm	altered liver cells	Lehman, 1952a
		10 ppm		altered liver cells	
		50 ppm		moderate liver damage	
		100 ppm		slight chronic poisoning	
		600 ppm		pronounced liver damage, Nervous tremors	
Dog	3 years	10 mg/kg/day (in corn oil)	10 kg/day	no adverse effect	Lehman, 1952b
		50 mg/kg/day (in corn oil)		died	
		80 mg/kg/day (in corn oil)		died	
Man	21.5 months	0.5 mg/kg/day		fat storage to 105-659 ppm	Hayes, 1963

[This compound is an animal carcinogen.]

METHOXYCHLOR

I. INTRODUCTION

Methoxychlor, or 2,2-*bis*-(p-methoxyphenyl)-1,1,1-trichloroethane, was introduced as an insecticide in 1945. It is a close relative of DDT and has been used as an insecticide of very low mammalian toxicity for home and garden, on domestic animals for fly control, for elm bark-beetle vectors of Dutch elm disease, and for blackfly larvae in streams. Methoxychlor is registered for about 87 crops--alfalfa; nearly all fruits and vegetables; corn, wheat, rice, and other grains; beef and dairy cattle; and swine, goats, and sheep--and for agricultural premises and outdoor fogging. Domestic use of methoxychlor as a substitute for DDT is increasing and is estimated at 10 million pounds a year (NAS 1975).

Methoxychlor is produced by condensing anisole with chloral. About 88% of the technical product is the p,p'-isomer, and the principal impurity is the o,p-isomer. The p,p'-isomer is soluble in water at 0.26 ppm at 25°C (Kapoor *et al.*, 1970). Its major breakdown product, 2,2-*bis*-(p-hydroxyphenyl)-1,1,1-trichloroethane, is soluble in water at 76 ppm (Kapoor *et al.*, 1970).

The half-life of Methoxychlor in water is about 46 days. No residues of Methoxychlor were detected in 500 samples of finished drinking water from the Mississippi and Missouri Rivers (Schafer *et al.*, 1969) or in 191 samples from Hawaii. No Methoxychlor was found in the New Orleans drinking-water survey (USEPA, 1974a).

The average daily intake of Methoxychlor in the human diet over a 6-year period (1965-1970) was less than 0.001 mg (NAS, 1975). The maximal U.S. residues found were: dairy products, 0.006 ppb; grain and cereal, 0.003 ppb; leaf vegetables, 0.031 ppb; and fruits, 0.023 ppb (USEPA, 1976e).

Tolerances of Methoxychlor on more than 80 raw agricultural commodities range from 1 to 100 ppm, with most at 14 ppm.

The EPA has set an interim standard for Methoxychlor in finished water for 0.1 mg/liter (USEPA, 1975i).

II. METABOLISM

Unlike DDT, Methoxychlor is not highly bioconcentrated and stored in animal fatty tissue. For example, when Methoxychlor was fed to rats at 25 ppm, no fat storage was detected; at 100 ppm, only 1 ppm was stored; and at 500 ppm, storage in 4 weeks reached 36 ppm in males and 17 ppm in females, but rapidly declined, and no Methoxychlor could be detected in fat 2 weeks after Methoxychlor feeding was stopped (Kunze *et al.*, 1950). In contrast, DDT fed at 1 ppm under identical conditions was stored at 13 ppm in male and 18 ppm in female rats (Lang *et al.*, 1950). When green sunfish, *Lepomis cyanellus* and *Tilapia mossambica*, were exposed to Methoxychlor in water at 0.01 ppm for 31 days, the body residues were 2.7 and 2 ppm, compared with 40.2 and 106 ppm for DDT at the same concentration (Reinbold *et al.*, 1971).

Methoxychlor is rapidly excreted by animals as the mono-phenol and *bis*-phenol derivatives and their conjugates. When radiolabeled Methoxychlor was administered orally to mice, 98.3% was eliminated in 24 h (Kapoor *et al.*, 1970). *Tilapia mossambica* exposed to Methoxychlor at 0.003 ppm in water for 12 days contained 8 ppm; they were then transferred to clean water and contained only 0.0001 ppm after 15 more days (Reinbold *et al.*, 1971).

Methoxychlor is readily *O*-demethylated by microsomal oxidase enzymes in mouse liver (Kapoor *et al.*, 1970) to form principally 2-(*p*-hydroxyphenyl-2-(*p*-methoxyphenyl)-1,1,1-trichloroethane and 2,2-*bis*-(*p*-hydroxyphenyl)-1,1,1-trichloroethane (Kapoor *et al.*, 1970). These--with 2,2-*bis*-(*p*-hydroxyphenyl)-1,1-dichloroethane (produced by reductive dechlorination), 4,4'-dihydroxybenzophenone, and 4,4'-dihydroxydiphenylacetic acid--are the principal excretory products in mice (Kapoor *et al.*, 1970) and fish (Rienbold *et al.*, 1971). All these were found as degradation products in a laboratory model ecosystem, as well as traces of Methoxychlor ethylene (Kapoor *et al.*, 1970). In this system, Methoxychlor had an ecologic magnification of 1,545 compared with 84,500 for DDT, and a biodegradability index of 0.94, compared with 0.015 for DDT (Kapoor *et al.*, 1973). Thus, Methoxychlor differs substantially from DDT in the presence of the methoxy degradophores that make it biologically much more degradable.

III. HEALTH ASPECTS

A. Observations in Man

There is no conclusive evidence of Methoxychlor intoxication in humans.

B. Observations in Other Species

Acute Effects. Methoxychlor is one of the safest of all insecticides. The oral LD_{50} in rats is over 6,000 mg/kg; that in mice is 2,900 mg/kg; that in monkeys is over 2,500 mg/kg. The dermal LD_{50} in rabbits is over 2,800 mg/kg (USEPA, 1976a). The acute oral LD_{50} of 2,2-*bis*-(p-hydrophenyl)-1,1,1-trichloroethane, the principal metabolite, in mice is 600 mg/kg (Von Oettingen and Sharpless, 1946).

Chronic Effects. Methoxychlor fed to rats at 10,000 ppm was toxic, but fed at 5,000 ppm for 52 weeks produced mortality comparable with that in untreated controls. There was some growth retardation at 2,500 ppm and above, but no gross pathologic changes were found. No tremors were observed at any time (Haag *et al.*, 1950). Methoxychlor fed to rats for 2 years at 0.02% produced no abnormal gross pathology or histopathologic changes (Haag *et al.*, 1950). When fed to beagle dogs at 1, 2, and 4 g/kg/day over 6 months, Methoxychlor produced convulsions at the 2 and 4 g/kg and increased serum alkaline phosphatase and serum transaminase (Tegeris *et al.*, 1966). However, when fed at 300 mg/kg/day for 1 year, in another study, it had no observed effects on body weight, hematology, or histopathology (USEPA, 1976a).

Mutagenicity. In mutagenic evaluation with *Escherichia coli* WP 2TRY, Methoxychlor gave negative results (Ashwood-Smith *et al.*, 1972).

Carcinogenicity. Methoxychlor fed in FDA studies for 2 years to C_3He/FeJ and BALB/cJ mice at 750 ppm in the diet showed no significant difference in incidence of hepatocellular hyperplasia and hepatoma between controls and treated in mice. Testicular tumors were found in BALB/cJ mice, and it was concluded from histologic examination that Methoxychlor caused a significant increase in the incidence of this tumor in BALB/cJ mice, but not in C_3He/FeJ mice (USEPA, 1976a).

Reproduction. Rats fed Methoxychlor at 1,000 ppm in the diet had normal reproduction. At 2,500 ppm, fewer rats mated, and many did not produce litters. At 5,000 ppm, none of the rats had litters or implantation (Harris *et al.*, 1974). Further studies with 250 ppm through three generations showed no gross or histopathologic changes in any tissues from rats of the F_3 generation.

Because of the possible resemblance of Methoxychlor detoxication phenols to diethylstilbestrol, additional studies were made to evaluate chronic feeding of Methoxychlor for estrogenic effects. The results showed both no-adverse effect and uterine weight increase. The latter effect was found to be at least partially due to an unidentified contaminant in technical Methoxychlor (Tullner, 1961).

Teratogenicity. No available information.

IV. CONCLUSIONS AND RECOMMENDATIONS

Methoxychlor, a close relative of DDT, has very low mammalian toxicity. In a 2-year feeding study no adverse effect was observed at 200 ppm in rats. On the basis of these chronic data an ADI was calculated at 0.1 mg/kg/day. The available data on chronic toxicity and calculations of ADI are summarized in Table VI-25.

TABLE VI-25. Summary of Chronic Toxicity Data for Methoxychlor

Species	Duration of Study	Dosage Levels and No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest Minimal-Effect Level	Effect Measured	Reference
Mouse	2 yrs	750 ppm		No carcinogenesis, C_3H/HeJ Increased testicular tumors BALB/cJ	USEPA, 1976a
Rat	2 yrs	200 ppm	200 ppm (10 mg/kg/day)[c,d]	No adverse effect	Hodge *et al.*, 1950
Rat	6 wks	0.0 ppm, (17 animals)			Harris *et al.*, 1974
		1,000 ppm, (17 animals)		Normal reproduction	
		2,500 ppm, (20 animals)		Retarded reproduction	
		5,000 ppm, (25 animals)		Inhibited reproduction	
Dog (beagle)	6 months	0.0 ppm 1 g/kg/day (6 animals)		1/6 convulsions	Tegeris *et al.*, 1966
		2 g/kg/day (6 animals)		5/6 convulsions CNS effects, death	
		4 g/kg/day (6 animals)		6/6 convulsions, death	

Using an uncertainty factor of 100, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{10}{100} = 0.1 \text{ mg/kg/day (ADI)},\ 0.1 \times 70^{a} \times 0.1^{b} = 0.7 \text{ mg/liter.}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse-effect level.

[d] Assume weight of rat = 0.4 kg and average daily food consumption of rat = 0.02 kg.

BENZENE HEXACHLORIDE (BHC) AND LINDANE

I. INTRODUCTION

"Benzene hexachloride" (BHC) is the common name used to designate the mixed isomers of 1,2,3,4,5,6-hexachlorocyclohexane. "Hexachlorohexane" is the proper term for this compound; however, because it is more customary, the trivial name, "benzene hexachloride" (or BHC), will be used in this document.

BHC (technical grade) is a mixture of the eight possible isomers that constitute the different spatial arrangements of the six chlorine atoms on the trans- (or chair) form of the ring. Its composition approximates 65% α isomer, 11% β, 13 - 14% γ, 8 - 9% δ, and 1% ε. The lowest-melting-point (112.8 C) isomer, which is also the most reactive known, is that designated as the γ isomer. The commercial insecticide Lindane is defined as a product containing at least 99% γ isomer (the remainder being other BHC isomers). Technical BHC is prepared by photochlorination of benzene. Production of the γ isomer for Lindane is achieved by selective crystallization (Melnikov, 1971).

The different isomers have different solubilities in water and different vapor pressures: α, 10 mg/liter and 0.06 torr; β, 5 mg/liter and 0.17 torr; and γ, 10 mg/liter and 0.14 torr (Melnikov, 1971; NAS, 1975). The relatively high water solubility and vapor pressure of Lindane cause it to have relatively low persistence in the environment. Lindane has been detected in the finished water of Streator, Illinois at 4 μg/liter (USEPA, 1975j).

The EPA has set an interim standard for Lindane in finished water for 0.004 mg/liter (USEPA, 1975i).

The insecticidal properties of BHC were discovered and developed for commercial use in pest control beginning in 1942. When it was found that virtually all the insecticidal activity of BHC resided in the γ-isomer, major development of the latter as an insecticide itself was rapid. Lindane has been marketed under a large number of trade names as an insecticide. It has had major use in insect control in domestic and commercial settings, in numerous agricultural and silvicultural applications, and in dips, sprays, and dusts for livestock and pets. Recent U.S. production has been under 1 million pounds a year (NAS, 1975).

II. METABOLISM

Mammalian biotransformation of BHC isomers involves the formation of chlorophenols (trichlorophenol, tetrachlorophenol, and pentachlorophenol), which are excreted free and as conjugates of sulfuric and glucuronic acids (Grover and Sims, 1965; Freal and Chadwick, 1973). Freal and Chadwick (1973) hypothesized that Lindane is metabolized in the rat through a pentachlorocyclohexene to a series of trichlorobenzenes and tetrachlorobenzenes en route to the corresponding chlorophenols. In later work, however, Chadwick *et al.* (1975) established that Lindane is initially metabolized to a hexachlorocyclohexene intermediate, from which two tetrachlorophenols and three trichlorophenols are later derived. This mode of metabolism is apparently peculiar to the γ-isomer. Freal and Chadwick (1973) showed that pretreatment of rats with BHC isomers resulted in enhanced metabolism of Lindane to the chlorophenols; the effects decreased in the order α>δ>γ>>β.

Metabolism of isomers other than γ-BHC leads to trichlorophenols, not all identical with those formed from the γ-isomer; but apparently no tetrachlorophenol occurs. Mercapturic acid excretion has also been observed after administration of BHC isomers. This may be due in part to the glutathione-dependent dechlorination of chlorobenzenes otherwise formed during BHC degradation, which then gives rise to the chlorophenols (Freal and Chadwick, 1973). Portig *et al.* observed the direct glutathione-dependent conversion of α-BHC to a hydrophilic metabolite by a preparation of rat liver cytosol. This is similar to the known biodegradation of γ-BHC in insects, which is glutathione-dependent (Ishida and Dahm, 1965); the insect enzyme acts on α-BHC more readily than on γ-BHC, and the β-isomer is nonreactive. The mammalian enzyme activity is increased after pretreatment of the rat with α-BHC (Kraus *et al.*, 1973). Pentachlorobenzene and pentachlorophenol have so far been observed only as metabolites of Lindane in the rabbit (Karapally *et al.*, 1973). The eliminated products, the free and conjugated chlorophenols, are much less toxic than the parent isomers, and some are being considered separately as contaminants in water.

III. HEALTH ASPECTS

A. Observations in Man

Surveys of human tissue for organochlorine insecticide residues frequently show the presence of the most persistent, the β-isomer of BHC. In a study on the concentration of organochlorine residues in fat and liver of terminal patients, the only BHC isomer noted was the beta. Its concentration in cancer patients did not differ significantly from that in people dying from infectious or other diseases (Radomski et al., 1968). Chronic liver damage (cirrhosis and chronic hepatitis) has been found, in liver biopsy, in eight workers heavily exposed to BHC, DDT, or both for periods ranging from 5 to 13 years. As far as was feasible, other conditions, such as alcoholism, were excluded as the cause of the cirrhosis (Schuttmann, 1968).

Over 30 cases of exposure to BHC or Lindane and 21 cases of exposure to BHC and DDT followed by the development of aplastic anemia have been reported in the literature (Loge, 1965; West, 1967; Woodliff et al., 1966). No satisfactory animal model of that condition has been found and, despite efforts to study the question, a firm causal relationship betwenn Lindane or technical BHC exposure and aplastic anemia cannot be stated. Development of leukemia after Lindane exposure was reported for two cases (Jedlicka, 1958). That causal relationship is also inconclusive in relation to insecticide exposure.

B. Observations in Other Species

Acute Effects. Lindane is the most toxic of the isomers of BHC. It excites the central nervous system, producing hyperirritability, incoordination, convulsions, and death due to respiratory collapse. Its single-dose oral LD_{50} in rats is 88-300 mg/kg (Gaines, 1969; Riemschneider, 1949; Burkatskaya, 1959; Slade, 1945; Klosa, 1950; Woodward and Hagan, 1947; Cooper et al., 1951). The oral LD_{50} of technical BHC is 600-1,250 mg/kg; those of the other isomers are about 1,500 mg/kg (α) 2,000 mg/kg (β), and 100 mg/kg (δ) (Riemschneider, 1949; Burkatskaya, 1959; Slade, 1945; Klosa, 1950; Cooper, 1951). The wide range in observed LD_{50} for Lindane presumably results from differences in rates of absorption of various preparations of the material and variations in rates of detoxification and excretion under different experimental conditions. Single oral doses of 10-25 mg/kg in corn oil were fatal to beagles (Cited in USEPA, 1973b), and domestic animals were poisoned by similar amounts (Wasserman et al., 1960).

Subchronic and Chronic Effects. Klimmer (1955) administered daily doses of Lindane, at 32 mg/kg of body weight, by stomach tube to male and female rats for 6 months. He observed nervous symptoms, fatty degeneration of the liver and renal tubular epithelium, vacuolisation of the cerebral cells, and a marked increase in mortality. None of these effects was seen with a daily dose of 10 mg/kg during 17 months. Melis (1955) fed diets containing Lindane at 2, 3, 4, 5, or 10 ppm for 12 months to rats and found no abnormalities in general behavior, body weight, histology, or other characteristics.

Beagle dogs were not affected by Lindane in the diet at 7.5 mg/kg/day (Cited in USEPA, 1973b). Higher dosages produced central nervous system effects.

Under condition of chronic administration, the γ-isomer is considerably less toxic than the other principal isomers of technical BHC. Fitzhugh et al. (1950) conducted 2-year-rat feeding studies with the various isomers of BHC, using diets containing the α, β, and γ-isomers at 5 - 1,600 ppm. These experiments clearly showed that the γ-isomer was the least toxic, and the β-isomer, the most toxic. The organs injured were the liver and, to a lesser extent, the kidneys. In the case of Lindane, the lowest concentration causing significant liver changes was 100 ppm; no effect was noted below 50 ppm. Truhaut (1954) summarized data from 2-year feeding studies in rats with Lindane in the diet at 25, 50, and 100 ppm. At 25 ppm, no evidence of histologic changes in the liver or kidney or any other toxic effects were seen. At the higher concentrations, hypertrophy of the liver was observed, and, at 100 ppm, a slight degree of fatty degeneration. These findings and dose relationships were confirmed by other workers (Ortega et al., 1957). FAO/WHO (1967) accepted 25 ppm in the diet of rats as the maximal concentration causing no adverse effects.

The hypertrophic liver and fatty degenerative changes of liver at higher dosage are similar to those produced by other slowly metabolized organochlorine compounds. As might be expected, Lindane induces hepatic microsomal enzymes (Freal and Chadwick, 1973). That effect may proceed in time and dosage relationships the liver pathology already described (Hutterer and Schaffner, 1968).

Mutagenicity. In a dominant lethal assay, Lindane was administered to male mice as a single intraperitoneal dose of 12.5, 25, or 50 µg/kg (corresponding to one-eighth, one-fourth, or one-half of the LD_{50}), and the mice later mated with successive series of females during a 7-day period. No mutations were observed, nor were any reproductive effects noted (Cited in USEPA, 1973b). Host-mediated testing produced mutagenic rates too low to be considered positive (Cited in USEPA, 1973b). However, it has been claimed that Lindane in cell-culture media at 0.1-10 µg/ml affected the mitotic activity and the karyotype of human lymphocytes cultivated in vitro (Tsoneva-Maneva, et al., 1971). In general, published reports indicate that Lindane does not have significant mutagenic potential.

Carcinogenicity. An investigation in rats fed over a lifetime on diets containing technical BHC, α-BHC, β-BHC, or γ-BHC at 10-800 ppm did not show evidence of increased tumor incidence or carcinogenicity (Fitzhugh, *et al.*, 1950). In the same study, Lindane was also administered at 5-1,600 ppm as a solution in oil. The average life-span was significantly reduced when all compounds were given at 800 ppm and more, but the tumor incidence in animals receiving treatment was not greater than that in controls (Fitzhugh *et al.*, 1950). However, it should be noted that not all animals in the study underwent microscopic examination of organs. In a further experiment in which rats received diets containing γ-BHC at 25, 50, or 100 ppm for 2 years, no significant increase in tumor incidence was observed (Truhaut, 1954).

Prompted by epidemiologic evidence, however, and the very high use of BHC in Japanese agriculture, more recent investigations have been undertaken that have developed quite a different picture. Nagasaki *et al.* (1971, 1972a) showed hepatoma formation in all tested mice on diets containing technical BHC at 660 ppm; diets containing either 6.6 or 66 ppm did not produce tumors. As expected, no hepatic nodules or tumors occurred in 14 male controls; the spontaneous incidence of liver tumors in this strain of mice is reportedly very low.

In a later experiment, groups of male dd mice were fed the α, β, γ, or δ-isomer separately, each at 100, 250, or 500 ppm. The experiment was terminated at 24 weeks. Multiple liver tumors, up to 2.0 cm in diameter, were found in all animals given α-BHC at 500 ppm; whereas smaller nodules were found in nine of twenty mice given 250 ppm and no lesions were found in mice given 100 ppm. No tumors were produced with any dosage of the other three isomers or in a similar group of 20 control mice (Nagasaki *et al.*, 1972b).

Thorpe and Walker (1973) fed groups of male and female CF1 mice diets containing β-BHC at 200 ppm or γ-BHC at 400 ppm. The percentages of animals that had liver tumors were 24%, 73% and 93% in males and 23 percent, 43%, and 69% in females for the controls, 200-ppm β-BHC, and 400-ppm γ-BHC diets, respectively. Lung metastases were found in some males receiving β- and γ-BHC and in some females receiving γ-BHC. The incidence of other tumors was not increased by exposure to either isomer.

Coincidentally with the Thorpe and Walker study, another research group reported results of feeding groups of male CR/JO mice from 5 to 31 weeks old on diets containing technical BHC, pure α, pure β, pure γ, or a mixture of δ and ϵ at 600 ppm. Liver nodules were found in all groups except the β-group BHC (Goto, *et al.*, 1972). The tumors frequently appeared to be malignant in the case of animals administered diets containing α-BHC and the δ- and ϵ-BHC mixture. The findings were interpreted as indicating that α-BHC or its metabolites are most probably carcinogenic. In the same study, three Lindane metabolites, 1,2,4-trichlorobenzene, 2,3,5-trichlorophenol, and 2,4,5-trichlorophenol were administered for 6 months in the diet at 600 ppm; these treatments produced no hepatic tumors.

Further study by the Japanese researchers confirmed the high carcinogenicity of α-BHC and showed that combination of it with either β-, γ- or δ-BHC had no synergistic or antagonistic effect on the induction of tumors by α-BHC. Related studies showed that technical polychlorinatnd biphenyl (Kanechlore) promoted the induction of hepatic tumors by α-BHC and β-BHC; mice fed γ-BHC with or without PCB's did not show neoplastic changes in the liver (Ito *et al*., 1973).

The data on induction of liver tumors by γ-BHC in mice are seen to be somewhat contradictory. For example, Thorpe and Walker (1973) found γ-BHC to be somewhat tumorigenic in CF1 mice but the Japanese workers used other strains and found that they were not susceptible to tumorigenic action by γ-BHC (Nagasaki *et al*., 1971, 1972a, 1972b). The acute toxicity of technical BHC and BHC isomers components also differs greatly among various mouse strains; the CF1 strain is particularly susceptible to acute poisoning (Miura *et al*., 1974). Such toxicity differences may be related to different rates of metabolism of BHC; if so, the tumorigenic effects may also be so related.

The first report of tumorigenic activity of γ-BHC in rats was made by Nagasaki *et al*. in 1972 . Three groups of Wistar rats (seven per group) were fed diets containing each BHC isomer at 250, 500, and 1,000 ppm. In rats sacrificed at 24 weeks, the increased liver weight was recognised only in the 500 and 1,000 ppm groups with absence of hepatoma. At 40 weeks, one of seven rats in the 1,000 ppm γ-BHC group showed a hepatoma, which was 1.5 cm in diameter. Three other animals of the same group showed clear hypertrophic nodules without signs of malignant tumor, as did other dosage and isomers groups. On the basis of these findings, it was concluded that γ-BHC was carcinogenic in rats, but that rats were less sensitive than mice.

A study of hepatocellular carcinoma development in rats treated with various isomers of BHC was recently published (Ito *et al*., 1975). Male Wistar-derived rats were administered BHC isomers in the diet for 72 weeks. Each treatment group included 18-24 animals. The dietary treatment levels were: α-BHC, 500, 1000, and 1500 ppm; β-BHC, 500 and 1000 ppm; γ-BHC, 500 ppm; δ-BHC, 500 and 1000 ppm. No neoplastic changes or other abnormal findings such as oval cell infiltration, fatty changes, fibrosis, or bile duct proliferation of the liver were observed in groups receiving 100 ppm of any isomer, but relative liver weight was increased in all groups receiving 500 ppm of any isomer, but relative liver weight was increased in all groups except those treated with 500 ppm α-BHC. Tumors developed only in the livers of rats in groups given α-BHC. In a group treated with 1500 ppm α-BHC for 72 weeks, the liver increased in weight due to tumor growth; in 10 of 13 rats it had a slightly irregular surface with many nodules up to 2.0 cm in diameter. In groups, 12 out of 16 rats that received 1000 ppm α-BHC for 72 weeks, and 5 out of 12 that received 1000 ppm α-BHC for 48 weeks, developed liver tumors. No metastases were seen. No liver tumors developed in other dietary groups, and no tumors were seen in other organs of any experimental animals.

Reproduction. Charles River C.D. rats receiving Lindane at 25, 50, and 100 ppm continuously in the diet during a three-generation study showed normal reproduction, with respect to litter size, breeding rate, and birth weight in all generations. No malformations were found. The only effect observed was the expected liver hypertrophy with hepatocyte enlargement (Cited in USEPA, 1973b).

Teratogenicity. No available data.

IV. CARCINOGENIC RISK ESTIMATES

α-, β-, and γ-BHC have produced dose-related liver tumors when given orally to mice and rats (Ito et al., 1973 and 1975, and Thorpe and Walker, 1973). For each compound the available sets of dose response data were individually considered as described in the risk section in the margin-of-safety chapter. Each set of dose response data was used to statistically estimate both the lifetime risk and an upper 95% confidence bound on the lifetime risk and an upper 95% confidence bound on the lifetime risk at the low-dose level. These estimates are of lifetime human risks and have been corrected for species conversion on a dose-per-surface-area basis. The risk estimates are expressed as a probability of cancer after a lifetime consumption of 1 liter of water per day containing Q/ppb of the compound of interest. For example, a risk of $1X10^{-6}$ Q implies a lifetime probability of $2X10^{-5}$ of cancer if 2 liters/day were consumed and the concentration of the carcinogen was 10 ppb (i.e. Q=10). This means that at a concentration of 10 ppb during a lifetime of exposure this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the U.S. is taken to be 220 million people, this translates into 4400 excess lifetime deaths from cancer or 62.8 per year. Since several data sets are typically available the range of the low-dose risk estimates are reported.

For α-BHC at a concentration of 1 μg/liter (Q=1) the upper 95% confidence estimate of risk for man would fall between 2.2 to 6.5×10^{-4}Q.

For β-BHC at a concentration of 1 μg/liter (Q=1) the estimated risk for man would be from 1.3 to 3.5×10^{-5} Q. The upper 95% confidence estimate of risk at the same concentration would be between $2.5-5.8\times10^{-6}$ Q.

For Lindane at a concentration of 1 μg/liter (Q=1) the estimated risk for man would be from 3.3 to 8.1×10^{-6} Q. The upper 95% confidence estimate of risk at the same concentration would be from $5.6-13\times10^{-6}$

V. CONCLUSIONS AND RECOMMENDATIONS

The chronic toxicity of the BHC isomers is clearly related to the tumorigenic effects so far observed only in rodents. The isomer is the most strongly implicated; its activity is sufficient to account for the degree of hepatoma formation observed with technical BHC administration in mice. Lindane is a weaker tumorigen in mice, and is so far a questionable tumorigen in the rats.

As of 1972, the FAO/WHO ADI for Lindane was set at 0.0125 mg/kg/day. Later, that value was reduced to 0.001 mg/kg/day and held under temporary status because of the newer data concerning carcinogenicity. A full-scale reevaluation of the chronic toxicity of Lindane is scheduled for 1977 by the FAO/WHO. The EPA has recently announced plans to issue a presumptive notice that Lindane is too hazardous for continued registered use, with the intention of reevaluating its administrative position on this insecticide.

In light of the above and taking into account the carcinogenic risk projections it is suggested that very strict criteria be applied when limits for BHC isomers are established. The available chronic toxicity data are summarized in Table VI-26.

TABLE VI-[illegible]. Summary of Chronic Toxicity Data for BHC Isomers

Chemical form and animal species	Duration of study	Dosage levels & No. of animals per group	Highest no-adverse effect level or lowest minimal effect level	Effect measured	Reference
RAT					
BHC (tech)	approx. 2 yrs.	10,50,100,800 ppm (10M, 10F)	[illegible] ppm	Reduced lifespan, no increased tumor incidence	Fitzhugh, et al., 1950
α-BHC, β-BHC	approx. 2 yrs.	10,50,100,800 ppm (10M, 10F)	[illegible] ppm		
γ-BHC	approx. 2 yrs.	5,10,50,100,400,800,1600 ppm (10M, 10F)	[illegible] ppm		
γ-BHC	2 years	25,50,100 ppm	100 ppm	No increase in tumor incidence	Truhaut 1974
α-BHC	72 weeks	500,1000,1500 ppm (13-24)	500 ppm	Liver hypertrophy (nodular hyperplasia, carcinoma at 1000 and 1500 ppm)	Ito et al. 1975
β-BHC	72 weeks	500,1000 ppm	500 ppm	Liver hypertrophy	
γ-BHC	72 weeks	500 ppm	500 ppm	Liver hypertrophy	
δ-BHC	72 weeks	500,1000 ppm	1000 ppm	Liver hypertrophy	
MOUSE					
BHC (tech)	24 weeks	6.6,66,660 ppm (20M, dd strain)	660 ppm	Hepatomas (20/20)	Nagasaki et al., 1971, 1972a
α-BHC	24 weeks	100,250,500 ppm (20M, dd strain)	250 ppm	Hepatic nodules (9/20), Tumors at 500(20/20)	Nagasaki et al., 1972b
β-BHC	24 weeks	100,250,500 ppm (20M, dd strain)	500 ppm	No adverse effect	
γ-BHC	24 weeks	100,250,500 ppm (20M, dd strain)	500 ppm	No adverse effect	
β-BHC	110 weeks	200 ppm (30M,30F;CF1 strain)	200 ppm	Hepatic tumors, lung metastases	Thorpe & Walker 1973
γ-BHC	110 weeks	400 ppm (29M,29F;CF1 strain)	400 ppm	Hepatic tumors, lung metastases	
BHC (tech)	26 weeks	600 ppm (20M;ICR-JCL strain)	600 ppm	Hepatic nodules, tumors	Goto, et al., 1972
α-BHC	26 weeks	600 ppm (20M;ICR-JCL strain)	600 ppm	Hepatic tumors, lung	
β-BHC	26 weeks	600 ppm (20M;ICR-JCL strain)	600 ppm	Hepatic tumors, lung	
δ-BHC	26 weeks	600 ppm (20M;ICR-JCL strain)	600 ppm	Hepatic tumors, lung	
γ-BHC	26 weeks	300,600 ppm	300 ppm	No adverse effect	
α-BHC	24 weeks	50,100,250 ppm (20M,dd strain)	100 ppm	Liver hypertrophy (hyperplasia, tumors at 250)	Ito, et al.
β-BHC	24 weeks	50,100,250 ppm (20M,dd strain)	250 ppm	Liver hypertrophy	
γ-BHC	24 weeks	50,100,250 ppm (20M,dd strain)	250 ppm	Liver hypertrophy(cellular)	
γ-BHC	80 weeks	12.5,25,50 ppm (? [illegible] strain)	50 ppm	No adverse effect	Herbst, et al., 1975

These compounds are animal carcinogens.

KEPONE

I. INTRODUCTION

"Kepone" is the trade name of decachlorooctahydro-1,3,4-metheno-2H-cyclobuta(cd)pentalen-2-one; its common name is "chlordecone," as designated by the International Standards Organization. Kepone was introduced in 1958. More recently it has been produced solely by the Life Science Products Company for Allied Chemical in Hopewell, Virginia, with the total output purchased by Allied Chemical. The Hopewell plant was closed in July 1975, when a number of its workers were found seriously ill. In August 1975, the EPA ordered that sales and use of the compound be stopped and prohibited further manufacture.

Kepone was registered for the control of root-borers on bananas with a residue tolerance of 0.01 ppm. This constituted the only food or feed use of Kepone. Nonfood uses included wireworm control in tobacco fields and bait to control ants and other insects in indoor and outdoor areas.

The U.S. production of Kepone for 1974 and 1975 was approximately 850,000 lb/year (Anonymous, 1976), and 99.2% of this was exported to Latin America, Europe, and Africa. The remaining 0.8% was used in the United States for ant and roach traps or baits.

Kepone was made by the dimerization of hexachlorocyclopentadiene in the presence of sulfur trioxide, followed by hydrolysis of the sulfonated intermediate to kepone (Brooks, 1974). The technical product (over 90% pure) sublimes at 350°C (Spencer, 1973); it is relatively soluble in water (0.4% at 100°C), compared with most chlorinated hydrocarbon pesticides.

Residual of Kepone has not been investigated in Market Basket Studies by the FDA. Kepone was not found in adipose tissue of humans in the monitoring programs of the Technical Services Division, Office of Pesticide Programs, EPA.

II. METABOLISM

Kepone is very stable in the environment. No degradation products have been reported, although ultraviolet produced dechlorinated products in a laboratory study (Alley et al., 1974). No metabolic products have been reported; cows fed 5.0 ppm in the diet for 60 days excreted 90 ppb of Kepone in milk 35 days after cessation of treated feeding (Smith and Arant, 1967).

III. HEALTH ASPECTS

A. Observations in Man

Kepone came to public attention after Life Science Products Company, which produced Kepone, was closed down when many employees became seriously ill with such afflictions as tremors, nausea, dizziness, impaired vision, and impotence. According to an internal report submitted to the Director of the Center for Disease Control by the Cancer and Birth Defects Division, Bureau of Epidemiology, Public Health Service, between March 1974 and July 1975, 62 (55%) of 113 worker at the plant had clinical findings that included nervousness, weight loss, pleuritic and joint pains, oligospermia, tremor, opsoclonia, and ataxia. Kepone was found in the blood of all 32 current employees, at 0.165 - 26 ppm. These were the first recorded cases of Kepone poisoning in humans. Illness incidence rates were highest for production workers and foremen and least for employees not working directly in production. The mean latency between start of employment and onset of symptoms was 6 weeks. Symptoms have persisted for as long as 6 months after employment was terminated (Public Health Service, 1976).

Companies using chlordecone have received Occupational Safety and Health Administration (OSHA) notices that this substance is hazardous and that its use should be strictly controlled. The OSHA suggested that worker exposure to Kepone be kept below 100 $\mu g/m^3$ of air for up to 10 h/day or 40 h/week, over a working lifetime. There is no specific OSHA standard for this chemical.

According to a report in the March 1976 issue of the Occupational Health Letter, Kepone is the cause of sterility in exposed human males, in addition to harmful effects on the nervous system and liver. Philip S. Guzelin, spokesman for a team of researchers at the Medical College of Virginia, reported on studies of 23 former industrial workers heavily exposed to Kepone who exhibited overt signs and symptoms of toxicity. In their investigations, the concentration of Kepone in whole blood has been in parts per million, or thousands of times greater than the minimal detectable concentration, and concentrations measured in biopsies of liver, muscle, and adipose tissue have been several times those in whole blood. Effective therapy for Kepone-associated toxicity is unknown. In the absence of data on the pharmacokinetics of Kepone and the mechanisms of its toxicity, rational treatment of exposed or afflicted people is impossible.

B. Observations in Other Species

Acute Effects. The acute oral LD_{50}, in corn oil solution, is 114 - 140 mg/kg in rats and 65 - 77 mg/kg in rabbits. The acute oral LD_{50} of the formulated product is about 95 mg/kg in male albino rats. The acute dermal LD_{50} is 345 - 375 mg/kg in rabbits (Martin, 1972). The characteristic effect of this compound was the development of DDT-like tremors. Acute rat inhalation studies of 10% Kepone dust with exposures 2 and 10 times as severe as those likely under agricultural conditions produced no pathologic or other outward effects in rats (USEPA, 1976b).

Chronic Effects and Carcinogenicity. Kepone has been reported to be oncogenic in rats (USEPA, 1961). Five groups of male and female albino rats were fed Kepone at 2, 5, 10, 25, 50, and 80 ppm for up to 2 years. Oncogenic effects appeared only in rats receiving Kepone in their diets for 1 - 2 years. None of 23 control rats examined developed hepatocellular carcinomas. Among the seven male rats fed at 25 ppm, liver lesions in one rat were diagnosed as hepatocellular carcinoma by pathologists and "evolving carcinoma" by one pathologist, who also found "evolving carcinoma" in a second male rat at this dosage. Among the 16 female rats that survived at 10 ppm, liver lesions in three were diagnosed as hepatocellular carcinoma by one pathologist. Among the nine female rats that survived at 25 ppm, liver lesions in one were diagnosed as "evolving carcinoma" by one pathologist (U.S. Dept. of Transportation 1976). Tremors developed, ranging from slight at 25 ppm to severe at higher dosages.

The carcinogenesis bioassay data prepared by NCI (1976) show the oncogenic effects of chlordecone on both sexes of Osborne-Mendel rats and B6C3F1 mice. Chlordecone was administered orally at average dosages ranging from 8 to 26 ppm for rats and from 20 to 40 ppm for mice for 80 weeks. The mice were sacrificed after 90 weeks, and the rats after 112 weeks; moribund animals were sacrificed and necropsied. Clinical signs of toxicity were observed in both species, including generalized tremors and dermatologic changes. None of the 225 control rats developed hepatocellular carcinomas. Fourteen of the 48 male control mice developed hepatocellular carcinomas. Pathologic diagnosis revealed a statistically significant increase ($p < 0.05$) in the incidence of hepatocellular carcinomas in rats fed an average of 24 ppm (males) and 26 ppm (females) and in mice fed an average of 20 and 23 ppm (males) and 20 and 40 ppm (females). Extensive hyperplasia of the liver was also reported in both species (NCI, 1976).

Reproduction. It has been reported in the literature that the administration of sublethal dosages of Kepone to male and female mice caused interference with the reproductive process.

Huber (1965) reported that the major physiologic effects of ingestion of sublethal dosages by laboratory mice, exclusive of the liver and tremor syndrome, involved the reproductive processes. The reproductive capacity of treated animals was inhibited or severely reduced. The females were largely responsible for the reduced reproduction. Data showed that the female hormonal system was disturbed. In a separate and independent mouse reproduction study (Good et al., 1965), authors showed that the reproduction in mice was reduced at all dosages used (10.0-37.5 ppm); both the size and the number of litters were decreased. Increased dosage resulted in increased effects. The reproductive effects of Kepone in rats have apparently not been tested.

Mutagenicity and Teratogenicity. There does not appear to be data on the mutagenic and teratogenic properties of Kepone.

IV. CARCINOGENIC RISK ESTIMATES

Kepone has produced dose-related hepatomas when fed to mice and rats (NCI, 1976). The available sets of dose response data were individually considered as described in the risk section in the margin of safety chapter. Each set of dose response data was used to statistically estimate both the lifetime risk at the low dose level. These estimates are of lifetime human risks and have been corrected for species conversion on a dose-per-surface-area basis. The risk estimates are expressed as a probability of cancer after a lifetime consumption of 1 liter of water per day containing Q/ppb of the compound of interest. For example, a risk of $1X10^{-6}$ Q implies a lifetime probability of $2X10^{-5}$ of cancer if 2 liters per day were consumed and the concentration of the carcinogen was 10 ppb (i.e. Q=10). This means that at a concentration of 10 ppb during a lifetime of exposure this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the U.S. is taken to be 220 million people, this translates into 4400 excess lifetime deaths from cancer or 62.8 per year. Since several data sets are typically available the range of the low-dose risk estimates are reported.

For Kepone at a concentration of 1 μg/liter (Q=1) the estimated risk for man would be between $3.2-6.0X10^{-6}$ Q. The upper 95% confidence estimate of risk at the same concentration would be from 1.4 to $8.0X10^{-6}$ Q.

V. CONCLUSIONS AND RECOMMENDATIONS

Kepone is a very toxic compound and is persistent in the environment. Test results clearly suggest that liver lesions, including cancer, were induced in both sexes of rats and mice fed chlordecone. In addition, the time to detection of the first hepatocellular carcinoma observed at death was shorter for treated than for control mice and, in both sexes and both species, it appeared inversely related to the dose.

In light of the above and taking into account the carcinogenic risk projections it is suggested that very strict criteria be applied when limits for Kepone in drinking water are established. The available chronic oral toxicity data are summarized in Table VI-27.

Apparently, little is known about the pharmacokinetics of Kepone and its mechanisms of toxicity. There is a pressing need for systematic investigation of the absorption, distribution, biotransformation, and excretion of Kepone in humans and experimental animals, to gain an understanding of its toxicity and to provide a basis for rational therapy.

There is also very little information on the environmental transport mechanisms of Kepone and its degradation products, its persistence, and its degradation in soil. Kepone residues have been found in food crops grown in rotation with Kepone-treated tobacco.

TABLE VI-27. Summary of Chronic Toxicity Data for Kepone (Chlordecone)

Species	Duration of study	Dosage levels and No. of animals per group	Highest no-adverse-effect level or lowest-minimal-effect level	Effect Measured	Reference
Rat	2 yrs	0, 5, 10, 25, 50, 80 ppm in diet (40 males and 40 females)	5 ppm (0.25 mg/kg/day)	No hepato-cellular carcinomas	EPA, 1961
Rat	112 wks	8 ppm (50 males) 24 ppm (44 males) 18 ppm (49 females) 26 ppm (49 females)	8 ppm (0.4 mg/kg/day)	Hepatocellular carcinomas appeared	NCI, 1976
Mice	90 wks	20 ppm (48 males) 23 ppm (49 males) 20 ppm (50 females) 40 ppm (49 females)	20 ppm	Hepatocellular carcinomas appeared	NCI, 1976

(This compound is an animal carcinogen.)

TOXAPHENE

I. INTRODUCTION

Toxaphene, a complex mixture of largely uncharacterized chlorinated camphene derivatives, is the most heavily used and least understood organochlorine insecticide. The major reason that so little is known about either its structure or its metabolism is its complex nature: it is a mixture of at least 175 compounds, of which the structures of fewer than 10 are known (Casida, et al. 1974).

Toxaphene is widely used as a foliage insecticide on a variety of food, feed, and fiber crops (USEPA, 1974c). A tolerance of 7 ppm was established in 1950 for a variety of crops. More recently, tolerances of 5, 3, and 2 ppm have been established for small grains, for cotton seed, and for bananas and soy beans, respectively. In addition, there is a temporary tolerance of 7 ppm for residues in or on sugar beets and sunflower seeds. Similar foreign tolerances have also been established. A tolerance of 7 ppm for residues of Toxaphene in the fat of meat has also been established. Other regulations have established interim tolerances for Toxaphene residues in or on alfalfa at 1 ppm and in milk at 0.05 ppm.

Like many organochlorine insecticides, Toxaphene is known to be somewhat persistent in the environment, particularly in soil. The EPA has set an interim standard for Toxaphene in finished water for 0.005 mg/liter ($C_{10}H_{10}Cl_8$-Technical chlorinated camphene, 67-69% chlorine) (USEPA, 1975i).

II. METABOLISM

Very little is known about the metabolism of Toxaphene in animals. In the rat, 52.6% of an oral dose of $[^{36}Cl]$Toxaphene was excreted within 9 days (Crowder and Dindal, 1974). Approximately 37% was found in the feces, and 15% in the urine. On extraction, most of the radioactivity occurred in the water fractions of urine and feces as ionic chloride. Animals given a second dose on the ninth day excreted Toxaphene in a similar manner, except that chlorine-36 excretion in feces was reduced. Less than 10% of the dose was found in selected tissues and organs 1 day after treatment.

Toxaphene has been found in milk of dairy cows given 20-140 ppm in the feed (Claborn et al., 1963). At lower concentrations, Zweig et al. (1963) reported that the amount of toxaphene in milk was less than 0.03 ppm. When the animals were removed from the toxaphene diets, the milk became uncontaminated within 2 weeks.

III. HEALTH ASPECTS

A. Observations in Man

Although some cases have been reported, acute Toxaphene poisoning in humans is rare. When Toxaphene was introduced, four cases of poisoning by ingestion in children under 4 years old were reported (McGee *et al.*, 1952). The same study contained a description of severe toxaphene poisoning in adults after its misuse in agriculture. The authors estimated that three patients ingested toxaphene at 9.5 - 47 mg/kg.

Aside from accidental poisoning, human volunteers have participated in Toxaphene toxicity studies. In one study, 50 human volunteers inhaled mist containing Toxaphene at 0.0004 mg/liter for 10 min/day for 15 days; there were no subjective or objective results (USEPA, 1974c). In another study, a mist containing Toxaphene at 0.25 mg/liter of air was inhaled by 25 people for 30 min/day for 13 days; there was no evidence of local or systemic toxicity (USEPA, 1974c).

B. Observations in Other Species

Acute Effects. Acute toxicity studies with Toxaphene have involved oral, dermal, intravenous, intraocular, and inhalation exposure. The toxicity of toxaphene is influenced by the solvent or vehicle used. When administered orally as a solution or emulsion, it is more toxic in a digestible vegetable oil than in an oil like kerosene. Toxicity of Toxaphene by skin absorption is much less from an inert dust than from an oily solution. The acute oral LD_{50} is 90 mg/kg in male rats and 80 mg/kg in female rats; the acute dermal LD_{50} is 1,075 mg/kg in male rats and 780 mg/kg in female rats (Gaines, 1960).

Administration of a 20% solution of Toxaphene in kerosene to the eyes of rabbits and guinea pigs for 14 consecutive days produced mild irritation of the eyelids with loss of hair around the eyelids. The eyes were not injured, and the irritation in the eyelid was abated within 10 days (USEPA, 1974c). In acute inhalation studies, 40% Toxaphene dust at 3.4 g/liter of air killed approximately half the exposed rats within 1 h.

Subchronic and Chronic Effects. Ortega *et al.* (1957) have studied the subchronic toxicity of Toxaphene in small groups of rats fed 50 and 200 ppm in the diet for 9 months. No clinical signs of toxicity or inhibition of food consumption or growth rate were evident. However, only the liver, spleen, and kidneys were examined histologically. There was no apparent damage to the kidneys or spleen, but 3 of the 12 rats that received 50 ppm showed slight liver changes, and 6 of the 12 rats fed 200 ppm showed distinct liver changes.

Degenerative changes in the kidney tubules and liver parenchyma have been reported in dogs fed Toxaphene at low dosages (Lacky, 1949); two dogs received 4 mg/kg/day (about 160 ppm) for 44 days, and two others received the same dosage for 106 days.

Chronic studies have been done in rats, guinea pigs, dogs, cattle, sheep, and rabbits. In rats fed at 25, 100, and 400 ppm in the diet for the conventional 2-year period, only the liver showed significant changes, at 100 and 400 ppm (Fitzhugh and Nelson, 1951).

Toxaphene was administered daily to dogs in a dry diet for 2 years. When it was fed at 40 ppm, there was slight degeneration of the liver; at 200 ppm, there was moderate degeneration of the liver(USEPA, 1976c).

Studies have also shown that, when Toxaphene is applied to the skin of many large animals (including cattle, sheep, goats, horses, and swine), adult animals can withstand higher dosages than immature animals. Also, applications of cotton patches treated with Toxaphene to the skin of 200 subjects caused no primary irritaion or sensitization.

Reproduction, Teratogenicity, Carcinogenicity, and Mutagenicity. A three-generation reproductive study was conducted, according to currently accepted protocol for rats, with Toxaphene at 20 and 100 ppm (Kennedy et al., 1973). No differences between control and Toxaphene-treated animals were reported, with respect to reproduction, performance, fertility, lactation, or viability, size, and anatomic structure of progeny. In mutagenicity studies, occurrence of mutagenic effects among the controls and the animals treated with Toxaphene were similar. No evidence of carcinogenic action was reported in any of the chronic-toxicity studies previously undertaken.

IV. CONCLUSIONS AND RECOMMENDATIONS

Toxaphene is a widely used organochlorine insecticide that apparently has not caused a great deal of environmental harm, although it has been used in agriculture for many years. Because it is a complex mixture of uncharacterized camphene derivatives, very little is known about its metabolism in plants or other higher organisms. Considerable information is available, however, on its toxicity in laboratory animals and various aquatic organisms. An ADI at 0.00125 mg/kg/day was calculated on the basis of the chronic toxicity data. The available toxicity data and calculations of ADI are summarized in Table VI-28.

A summary of the results of examination of over 100,000 samples of raw agricultural commodities by the FDA between 1963 and 1969 (Duggan *et al.*, 1971) shows that Toxaphene residues are seldom present. Thus, the possibility that large quantities of Toxaphene residues could be found in drinking water is not great.

TABLE VI-28: Summary of Chronic Oral Toxicity Data for Toxaphene

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-Adverse-Effect Level or Lowest-Minimal Effect Level	Effect Measured	Reference
Rat	9 months	50 ppm (12 animals)		Slight liver change in animals	Ortega et al., 1957
Rat	9 months	200 ppm (12 animals)		Distinct liver change in 6 animals	Ortega et al., 1957
Dog	44 days	160 ppm (2 animals)		Change in kidney tubules	Lackey, 1949
Dog	106 days	160 ppm (2 animals)		and liver parenchyma	Lackey, 1949
Rat	2 years	25 ppm, 100 ppm and 400 ppm	25 ppm (1.25 mg/kg)[c,d] 100 ppm	No adverse effect liver change	Fitzhugh and Nelson, 1951

Using an uncertainty factor of 1,000, suggested no-adverse effect level in drinking water is calculated as follows:

$$\frac{1.25}{1000} = 0.00125 \text{ mg/kg/day (ADI)}; \ 0.00125 \times 70^{a} \times 0.1^{b} = 0.0088 \text{ mg/liter.}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse-effect level.

[d] Assume weight of rat = 0.4 kg and average daily food consumption of rat = 0.02 kg.

V. ORGANOPHOSPHATES

AZINPHOSMETHYL

I. INTRODUCTION

Azinphosmethyl, or O,O-dimethyl-S-4-oxo-1,2,3-benzotriazin-3(4H)-ylmethylphosphorodithioate (Guthion), is a contact organophosphorus insecticide used on a variety of fruit, vegetable, nut, and forage crops. It was first registered for use in 1956, and there are no nonagricultural uses.

It is estimated that 2.7 million pounds of azinphosmethyl were used in the United States in 1971 (National Academy of Sciences, 1975), vitrually all applied to crops. This amounted to approximately 2% of the insecticides used in that year. The prime areas for the use of azinphosmethyl were the Northeast and Pacific states, followed by the Midwest.

Azinphosmethyl is produced by the reaction of N-bromethylazimidobenzoyl with sodium dimethyldithiophosphoric acid. It is soluble in water at 33 ppm at 25°C. The products of hydrolysis depend on the pH of the medium, but hydrolysis generally results in cleavage of the S-methylaryl bond. At a pH of 5, the halflife is 8.9 h at 70°C and 240 days at 20°C (Melnikov, 1971).

In the only study found on the behavior of azinphosmethyl in water (Weiss and Gakstatter, 1965), its halflife in both laboratory and natural water systems was found to be 30 - 70 days at a pH of 5.1 - 8.4. The higher the pH, the less persistent the compound seemed to be.

The acceptable daily intake of azinphosmethyl has been established by the WHO/FAO at 0.0025 mg/kg. The tolerance established by the FDA in the United States is 2 ppm. The FDA's Market Basket Surveys for pesticide residues do not include azinphosmethyl, so its possible presence in food has not been studied.

II. METABOLISM

There is apparently no information in the literature on the metabolism of azinphosmethyl in mammalian systems.

III. HEALTH ASPECTS

A. Observations in Man

The anticholinesterase effects of azinphosmethyl were studied in human subjects by administering it at 7, 8, and 9 mg/day for 4 weeks. There were five test subjects per dosage and two controls. Cholinesterase was measured twice a week before and during exposure. None of the dosages produced any significant decrease in red-cell or plasma cholinesterase (Rider *et al.*, 1970).

There are no reported cases of human poisoning by azinphosmethyl in the literature.

B. Observations in Other Species

Acute Effects. Acute oral LD_{50}'s in rats of 7-13 mg/kg (Simmon *et al.*, 1969), 10-18 mg/kg (Neumeyer *et al.*, 1969), and 12 mg/kg (Crawford *et al.*, 1970) have been reported. Oral LD_{50}'s values of 11 and 13 mg/kg were reported for female and male rats, respectively (Gaines, 1960). The oral LD_{50} is 20 mg/kg in mice (Crawford *et al.*, 1970) and 80 mg/kg in guinea pigs (DuBois *et al.*, 1957). The higher LD_{50} in guinea pigs might be the result of slower conversion azinphosmethyl to its active oxygen analogue.

The toxicity by other routes is about the same as by the oral route. In rats, the subcutaneous LD_{50} is 9.25 mg/kg (Edery *et al.*, 1970), the intraperitoneal LD_{50} is 5.7 mg/kg in females and 11.6 mg/kg in males (DuBois *et al.*, 1957), and the dermal LD_{50} is 280 mg/kg (Simmon *et al.*, 1969). The intraperitoneal and subcutaneous LD_{50}'s in mice are similar.

Subchronic and Chronic Effects. Although there have been a number of studies of the effect of azinphosmethyl on *in vitro* and *in vivo* cholinesterase activity, none of these were designed to establish a no-adverse effect or minimal-effect dosage. DuBois *et al.* (1957) did establish that azinphosmethyl was a relatively weak *in vitro* cholinesterase inhibitor, the I_{50} being 2×10^{-4}*M*, 7.7×10^{-5}*M*, and 7.7×10^{-4}*M* for brain, submaxillary gland, and serum enzyme respectively. The oxygen analogue of azinphosmethyl, however, would be expected to be far more active in such an *in vitro* assay.

Azinphosmethyl was fed to postweaning Wistar rats at 5, 20, and 50 ppm for 2 years, with 60 of each sex in each dosage group. Twenty-three weeks after the beginning of the study, dosage of 2.5 ppm was added; after 47 weeks, the 50-ppm dosage was increased to 100 ppm. No adverse effects were observed in the

50-ppm group, but increasing the dosage to 100 ppm resulted in convulsive episodes in several animals and a consistent decrease in plasma and red-cell cholinesterase activity. The no-adverse effect dosage was determined to be 50 ppm (Worden *et al.*, 1973).

The same authors (Worden *et al.*, 1973) conducted a 2-year feeding study in dogs. Four cocker spaniels of each sex were fed 5, 20, and 50 ppm. Because no adverse effects were seen in the initial stages of the experiment, the dosage of 20 ppm was increased to 50 ppm, and the 50-ppm was increased to 100 ppm at 36 weeks. The 100-ppm dosage wa increased to 150 ppm at 57 weeks and to 300 ppm at 83 weeks. The dosage of 150 ppm was "well tolerated," but 300 ppm had adverse effects. Slight effects were noted at dosages above 20 ppm, so the no-adverse effect dosage, with cholinesterase decrease as the determining factor, was established as 20 ppm.

The WHO/FAO (1969) summarized proprietary data on rats and dogs in 2-year feeding studies. For rats, probably on the basis of the same study as later published by Worden *et al.* (1973), the no-adverse-effect dosage was established as 2.5 ppm (0.125 mg/kg/day) with plasma cholinesterase as the factor measured. For dogs, 5 ppm (0.125 mg/kg/day) was the no-adverse effect dosage when dogs were treated at 5, 10, 10, and 50 ppm in the diet. Serum cholinesterase and red-cell cholinesterase were the factors measured.

Mutagenicity. No reports on mutagenicity testing of azinphosmethyl could be found.

Carcinogenicity. Although not specifically designed to test carcinogenicity, the chronic toxicity studies of Worden *et al.* (1973) included observations on tumor incidence. There was no evidence that azinphosmethyl induced tumor formation, as the incidence of tumors was highest in the control group and lowest in the highest dosage azinphosmethyl group.

Reproduction. There are no studies of the effect of azinphosmethyl on reproduction in the open literature.

Teratogenicity. The chick embroyo test for teratogenic potential was negative for azinphosmethyl (Roger *et al.*, 1969). No terata were observed at dosages of 1 mg/egg or less.

There are no *in vivo* studies reported in the literature designed to test the teratogenic potential of the compound. However, in chronic-toxicity studies, there are no reports of abnormal offspring.

IV. CONCLUSIONS AND RECOMMENDATIONS

Azinphosmethyl is an organophosphorus insecticide whose principal application is in agriculture. Its mode of action is inhibition of the enzyme acetylcholinesterase. It has high acute toxicity, and ts chronic toxicity is moderate. Based on 2-year feeding studies in rats and dogs, an ADI at 0.0125 mg/kg/day was calculated. The available data and calculations of ADI are summarized in Table VI-29.

No specific methods for the analysis of azinphosmethyl in water have been reported. However, methods available for its determination in food materials and soils should be easily adaptable to water samples. Gas-chromatographic and other methods have been developed and are routinely applied for the analysis of azinphosmethyl. The sensitivity of these methods is well below that which would be required for the analysis of water samples with reasonable sample sizes.

There is a pressing need for studies on the metabolism of azinphosmethyl in mammalian systems. It is difficult to understand how a compound could have come to be so extensively used when so little is known of its fate in mammalian systems, as well as in soil and the environment.

Studies on the potential of azinphosmethyl for mutagenicity, teratogenicity, and carcinogenicity need to be conducted. There is almost nothing in the literature on the behavior of this compound in these respects.

Data on the behavior of azinphosmethyl in water and the likelihood of its appearing in drinking water are needed. Studies on its environmental transport would also be useful in this respect.

TABLE VI-29. Summary of Chronic Toxicity Data for Azinphosmethyl

Species	Duration of study	Dosage levels and No. of animals per group	Highest no-adverse-effect level or lowest-minimal-effect level	Effect Measured	Reference
Rats	2 yrs	0-50 ppm, orally 80 animals per group	50 ppm	No adverse effect	Worden *et al.*, 1973
Dogs	2 yrs	0-50 ppm, orally 8 animals per group	20 ppm	No adverse effect	Worden *et al.*, 1973
Rats	2 yrs		2.5 ppm (0.125 mg/kg/day)^{c,d}	No adverse effect	WHO/FAO, 1969
Dogs	2 yrs	0-50 ppm	5 ppm (0.125 mg/kg/day)^{c,d}	No adverse effect	WHO/FAO, 1969
Man	4 wks	7, 8, 9 mg/day 9 men per group	0.13 mg/kg/day^{a}	No adverse effect	Rider *et al.*, 1970

Using an uncertainty factor of 10, suggested no-adverse-effect levels in drinking water is calculated as follows:

$$\frac{0.125}{10} = 0.0125 \text{ mg/kg/day (ADI)},\ 0.0125 \times 70^{a} \times 0.1^{b} = 0.088 \text{ mg/liter.}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Test study from which to calculate suggested no-adverse-effect level.

[d] Assume average weight of rat = 0.4 kg and of dog = 10 kg; assume average daily food consumption of rat = 0.02 kg and of dog = 0.25 kg.

DIAZINON

I. INTRODUCTION

Diazinon, or *O,O*-diethyl *O*-(2-isopropyl-4-methyl-6-pyrimidinyl)-phosphorothioate, is a wide-spectrum organophosphorus insecticide and miticide extensively used in the United States on a wide variety of agricultural crops, ornamentals, domestic animals, lawns and gardens, and household pests.

In 1971, 3.2 million pounds of diazinon was used in the United States, accounting for about 2% of insecticide use (National Academy of Sciences, 1975). Most of this was on crops, with only small amounts used on livestock and for other purposes. The EPA estimates that diazinon use was 4.8 - 5.6 million pounds in 1974. According to the EPA, the peak of agricultural use of diazinon was in 1966, and it has been declining since. The two sources of data do not result in the same figures, but they do indicate the general range for the quantities of diazinon used. Major regions of agricultural use are the Pacific, Southeast, and Appalachian states. Large amounts of diazinon are also used in lawn and turf insect control in urban areas.

Diazinon is synthesized by a series of steps starting with isobutyronitrile, methanol, and methylacetoacetate. Technical diazinon is approximately 97 - 99% pure. Diazinon is soluble in water at 40 ppm at 20°C. Compared with other organophosphorus insecticides, diazinon is relatively stable to base and unstable to acid. The half-life at a pH of 3.14 is 0.5 day and at a pH of 10.9 is 6 days, compared with 185 days at a pH of 7.4 (Menzie, 1969).

A number of studies have indicated that diazinon is relatively nonpersistent in soil. Most diazinon applied is lost from the soil through chemical and biologic degradation within about 2 months of application (Getzin, 1966, 1968). There is little information available on the behavior of diazinon in an aquatic environment. Paris and Lewis (1973) reported that about 46% of the diazinon added to neutral aqueous solution remained after 2 weeks.

The acceptable daily intake of diazinon has been established by the WHO/FAO at 0.002 mg/kg. A large number of tolerances of diazinon in food have been established by the FDA. These generally range from as low as 0.75 ppm in vegetable crops to as high as 40 ppm in alfalfa as a forage crop. FDA Market Basket Surveys have found diazinon in about 2% of the food samples analyzed. In no case did the residue exceed the established tolerance limit (Duggan, 1968; Duggan *et al.*, 1971).

II. METABOLISM

The metabolism of diazinon has been reviewed by Fukami and Shishido (1972). Its metabolism is due principally to four enzyme systems: mixed function oxidases, in which diazinon is converted to its oxygen analogue and the isopropyl moiety and the ring methyl group may be hydroxylated; hydrolases or phosphatases, which cleave the aryl phosphate bond from the aromatic ring, producing phosphoric acids and pyrimidinols; glutathione-dependent transferases, which cleave the aryl phosphate bond and conjugate the resulting pyrimidine moiety with glutathione; and nonspecific esterases, which, again, produce phosphoric acids.

Most *in vivo* animal studies have demonstrated the production of diazoxon, hydroxydiazinon (the isopropyl secondary carbon is hydroxylated), isohyroxydiazinon (the ring methyl group is hydroxylated), and a propylenediazinon metabolite. These metabolites must all be considered potentially toxic, because they are neutral phosphorus esters. However, the activity of all has been shown to be lower than that of the parent compound. These metabolites are minor components in the urine and feces of treated animals. Most of the diazinon administered is accounted for in the urine of animals by the various cleavage products, which are not considered to be toxicologically active. In none of the studies of diazinon metabolism has cleavage of the ring been reported.

III. HEALTH ASPECTS

A. Observations in Man

The WHO/FAO (1967) reported that diazinon causes no toxicologic effects in man at 0.02 mg/kg/day. This determination resulted from treatment of human subjects at 0.02, 0.025, and 0.05 mg/kg/day for 37 days. Plasma cholinesterase decrease was measured.

B. Observations in Other Species

Acute Effects. The oral LD_{50} of diazinon in rats ranges from 66 to 800 mg/kg. This rather wide range may be accounted for by the use of various grades of purity of the material and different vehicles of administration. Bruce *et al.* (1955) reported an LD_{50} of 100-150 mg/kg for the 95% technical compound administered in corn oil. Schafer (1972) reported 150-220 mg/kg. Gaines (1969) reported 250 mg/kg in male and 285 mg/kg in female rats. The value of 800 mg/kg resulted from the use of "high purity" diazinon in a test with female rats (Sanderson and Edson, 1959). Several studies have demonstrated an effect of diet on the toxicity of diazinon (Boyd and Carsky, 1969; Boyd *et al.*, 1969). The LD_{50} ranged from 56 to 466 mg/kg, depending on the nutritional state of the animals used. Studies on the acute oral toxicity of diazinon to mice gave an LD_{50} of 82 mg/kg in females (Bruce *et al.*, 1955).

Intraperitoneal injection of diazinon in female rats gave an LD_{50} of 90 mg/kg (DuBois, 1961). Dermal toxicity in rats and rabbits was also determined. Gaines (1960) reported a dermal LD_{50} of 34 mg/kg in rats when the purified compound was administered in xylene, but 200 mg/kg female and 180 mg/kg in males with the impure material (Gaines, 1969). The dermal LD_{50} of the 25W formulation was greater than 4,000 mg/kg, expressed as the active ingredient (Bruce *et al.*, 1955).

Subchronic and Chronic Effects. Dogs were fed diazinon at 0.25, 0.75, and 75 ppm in the diet for 90 days. Each treatment group consisted of one male and one female; the control group had five dogs. Plasma cholinesterase and red-cell cholinesterase were measured. Red-cell cholinesterase was decreased only in the highest-dosage group, and plasma cholinesterase was decreased in the two higher groups. Thus, the no-adverse-effect dosage in this study was 0.25 ppm (Williams *et al.*, 1959).

Dogs were also used for an 8-month study in which diazinon was administered by gelatin capsule daily at 2.5, 5.0, 10.0, and 20.0 mg/kg. Three female and three male beagles were used for each group. Various hematologic factors and blood chemistry were measured monthly during the study and compared with preexposure data. Three of the dogs at the highest dosage died in the first month; one of the dogs at 10.0 mg/kg developed cholinergic symptoms, but recovered. There were no dose-dependent hematologic effects at any dosage. Unfortunately, cholinesterase decrease was apparently not measured in this study. For the factors measured, however, a no-adverse-effect dosage of 5.0 mg/kg could be concluded (Earl *et al.*, 1971).

Female Wistar rats were fed diets containing diazinon at 1, 5, 25, and 125 ppm for 15-16 weeks. There were 10 animals per group. Plasma cholinesterase and red-cell cholinesterase were measured throughout the test, and brain cholinesterase at termination. Red-cell cholinesterase was slightly decreased in the 5-ppm group, and no-adverse effects were observed at any time in the 1-ppm group (Edson and Noakes, 1960).

Other subchronic-toxicity studies were conducted in dogs (Bruce *et al.*, 1955) and miniature swine (Earl *et al.*, 1971), but neither study lends itself to the calculation of a no-adverse-effect dosage.

The WHO/FAO summarized proprietary data in the development of an acceptable daily intake in diazinon for rats (WHO/FAO, 1971) and dogs (WHO/FAO, 1965). A 90-day feeding study with rats at 0.5, 1, 2, and 4 ppm in which plasma cholinesterase decrease was the effect measured gave a no-effect-dosage of 2 ppm (0.1 mg/kg/day). For dogs treated with 0.02, 0.04, and 0.08 mg/kg/day for 31 days, the no-adverse-effect dosage was 0.02 mg/kg, when inhibition of plasma cholinesterase was used as the endpoint.

There are no chronic feeding studies with diazinon in the open literature. However, the WHO/FAO (1967) summarized a study in monkeys that resulted in the estimation of a no-adverse-effect dosage of 0.05 mg/kg/day. Monkeys were treated at 0.05, 0.5, and 5 mg/kg for up to 2 years. Inhibition of red-cell and plasma cholinesterase was measured.

No delayed neurotoxicity resulted from treatment of chickens subcutaneously with diazinon in peanut oil at 5 - 80 mg/kg (Durham et al., 1956).

Mutagenicity. Diazinon has not been extensively tested for its mutagenic properties. One study (Tsoneba-Maneva et al., 1969) on the effect of diazinon on mitosis in human lymphocytes reported chromosomal aberrations in 74% of the cells at 0.5 mg/ml. A dosage of 2.5 mg/ml produced a greater effect on mitosis than 0.5 and 5.0 mg/ml.

Carcinogenicity. Data from chronic oral-toxicity studies have not shown any oncogenicity resulting from diazinon.

Reproducion. No studies on the effect of diazinon on reproduction have been reported.

Teratogenicity. The 4E formulation of diazinon was administered to pregnant rats by gavage on days 9, 10, 8-12, or 12-15 of gestation. One day before parturition, the pups were delivered by Cesarean section and examined for abnormalities. None were found to be dose-related (Dobbins, 1967). However, a higher incidence of urinary malformations, hydronephrosis and hydroureter were observed in the multiple-dose animals than in the controls.

When diazinon was administered intraperitoneally to rats on day 11 of gestation at dosages sufficient to produce toxicity, it was found to be "slightly teratogenic" (Kimbrough and Gaines, 1968).

Robens (1969) studied the teratogenic effects of diazinon in hamsters and rabbits. Hamsters were treated at 0.125 and 0.25 mg/kg on day 6, 7, or 8 of gestation, and rabbits received either

7 or 10 mg/kg/day on days 5 - 15 of gestation. No terata were produced in either case.

Studies by Earl *et al.* (1973) on the effect of diazinon at 1, 2, or 5 mg/kg/day on dogs and 5 and 10 mg/kg/day on miniature pigs revealed a variety of gross abnormalities in some that may have been caused by diazinon.

V. CONCLUSIONS AND RECOMMENDATIONS

Diazinon is a widely used organophosphorus insecticide with applications in agriculture, homes and gardens, and structural pest control. It may well be used in situations that would lead to contamination of drinking water. The mode of action of diazinun, as with other organophosphorus insecticides, is inhibition of the enzyme cholinesterase. Its acute toxicity, however, in comparison with other organophosphates, is only moderate. Its metabolism is straightforward and leads to metabolites that have little toxic potential. Subchronic- and chronic-feeding studies are sufficiently complete and indicate little problem with the use of diazinon. An ADI was calculated at 0.002 mg/kg/day based on these data. The available data and calculations of ADI are summarized in Table VI-30.

Gas-chromatographic and thin-layer chromatographic methods are available for the analysis of diazinon in water. These methods require extraction of the diazinon from the water before analysis. Sensitivity thus depends on the size of the sample used. The anytical sensitivity of the methods, however, is adequate to detect concentrations lower than the recommended no-adverse-effect concentration in samples of reasonable size.

The data needed for the toxicologic evaluation of diazinon are fairly complete, and there is no pressing need for research to evaluate its safety. There is little information available on the actual presence or absence of diazinon in drinking water or in sources of drinking water. Studies on the environmental transport and persistence of diazinon would be useful in this respect.

TABLE VI-30. Summary of Chronic Toxicity Data for Diazinon

Species	Duration of Study	Dosage levels & No. of animals per group	Highest no-adverse effect level or lowest minimal effect level	Effect measured	Reference
Dogs	90 days	0.25-75 ppm in diet, 2 animals per group	0.25 ppm	No adverse effect	Williams et al. 1959
Dogs	8 months	0-20 mg/kg/day orally, 6 animals per group	5 mg/kg/day	No adverse effect	Earl et al., 1971
Rats	15-16 weeks	0-125 ppm in diet, 10 animals per group	1 ppm (0.05 mg/kg/day)	No adverse effect	Edson and Noakes, 1960
Rats	90 days	0-4 ppm in diet	2 ppm (0.1 mg/kg/day)	No adverse effect	WHO/FAO 1971
Dogs	31 days	0-0.08 mg/kg/day in diet	0.02 mg/kg/day^c	No adverse effect	WHO/FAO 1965
Monkeys	2 years	0-5 mg/kg/day	0.05 mg/kg/day	No adverse effect	WHO/FAO 1967
Man	37 days	0-0.05 mg/kg/day	0.02 mg/kg/day^c	No adverse effect	WHO/FAO 1967

Using an uncertainty factor of 10, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{0.02}{10} = 0.002 \text{ mg/kg/day (ADI)}, \; 0.002 \times 70^a \times 0.1^b = 0.014 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Calculation of suggested no-adverse-effect drinking water levels.

PHORATE AND DISULFOTON

1. INTRODUCTION

Phorate, or *O,O*-diethyl-*S*-[(ethylthio)methyl]-phosphorodithioate (Thimet ®), and disulfoton, or *O,O*-diethyl-*S*-[(2-ethylthio)ethyl]phosphorodithioate (Di-Syston ®), are closely related, systemic organophosphorus insecticides. The compounds differ from each other structurally only in the number of carbon atoms in the aliphatic side chain of the molecules, disulfoton having one more than phorate. Their properties and uses are quite similar. The principal uses for both compounds are in soil applications for the control of sucking insects.

There is only one report of the finding of a food containing disulfoton in the FDA's Market Basket Survey of prepared food (Corneliussen, 1970)--in a leafy vegetable containing 0.002 ppm, well below the tolerance limit. Phorate has not been found in food.

From the standpoint of total volume of use, both phorate and disulfoton must be considered as major insecticides. In 1971, [illegible].2 million pounds of phorate and 4.1 million pounds of disulfoton were used in the United States (National Academy of Sciences, 1975). Each represented 2% of the total insecticide used that year. Virtually all the phorate and disulfoton is used on crops, with less than 100,000 pounds (primarily disulfoton) being used for home and garden applications. The use of these compounds is growing steadily, with indications that further increase will occur as a result of DDT cancellation. The use of these compounds is most extensive in the south central states, followed by the western and north central areas. Only small amounts are used in the Southeast and Northeast.

Both compounds are synthesized commercially by straightforward procedures that give high yields of relatively pure products. Phorate is prepared by the reaction of *O,O*-diethylphosphorodithioic acid with formaldehyde and ethylmercaptan (Melnikov, 1971). It is soluble in water at 50 ppm. Disulfoton is prepared by the reaction of *O,O*-diethylphosphorodithioic acid with B-chloroethylethylsulfide (Melnikov, 1971). It is soluble in water at 25 ppm at 23°C. Both compounds are very susceptible to alkaline hydrolysis. Phorate has a half-life of 2 h in an aqueous solution at a pH of 8 and 70°C. It is much more stable in an acid medium (Sutherland *et al.*, 1966). Disulfoton is more resistant to hydrolysis, its half-life at a pH of 8 and at 70°C being 21.5 h; its half-life at a pH of 9 and at 70°C is 7.2 h (Muhlmann and Schrader, 1957).

The fate and significance of phorate and disulfoton in the environment have not been extensively studied. Both are highly toxic to the fish, crustaceans, and terrestrial wildlife that have been tested. However, there are no reported killings of wildlife, fish, or other aquatic organisms, probably because the use patterns of the compounds do not lead to contamination of the environments of such organisms. Information on the presence and persistence of phorate and disulfoton in water is unavailable.

Tolerances for phorate on many raw agricultural commodities have been established. These tolerances range from 0.1 to 3 ppm. Tolerances for disulfoton on 54 food and feed commodities have been established. These range from 0.1 to 12 ppm. The FAO/WHO has established a temporary acceptable daily intake for disulfoton--at 0.01 mg/kg--but not for phorate.

II. METABOLISM

Because the oxidative metabolites of disulfoton and phorate resemble the parent compounds in toxicity, it is important to consider the extent of their metabolism in mammalian systems and in the environment that would lead to human exposure to them.

In studies of phorate in rats, Bowman and Casida (1958) showed that hydrolysis products were the principal urinary components, consisting of diethylphosphorodithioic acid, diethylphosphorothioic acid, and diethyl phosphoric acid. In general, oxidative metabolites are not found as components of excretory products of animals treated with phorate. However, DuBois et al. (1950) used rat liver slices to show that phorate is converted by mammalian systems to its oxidative products. The major metabolites of phorate in blood after oral administration to rats have been shown to be phorate sulfoxide and phoratoxon sulfone.

Disulfoton follows essentially the same metabolic routes as phorate. Initial rapid conversion to the sulfoxide is followed by oxidation to the sulfone and oxidative desulfuration to the disulfotoxon sulfoxide and sulfone. Hydrolysis competes with the oxidative process to form the various phosphoric acids (Bull, 1965). Metabolism of disulfoton in plants parallels that in mammals. The oxidative metabolites are formed first, followed by hydrolysis to phosphoric acids.

III. HEALTH ASPECTS

A. Observations in Man

EPA accident files contain reports of 21 episodes of poisoning involving phorate for the period 1971-1973. Eleven were classified as agricultural, six as industrial, and four as having other causes. There have been no fatalities from phorate poisoning. There are no controlled studies of phorate in humans from which no-adverse-effect dosages could be derived.

Five human subjects were given disulfoton at 0.75 mg/kg for 30 days. Measurement of plasma and red-cell cholinesterase during the administration period and for 30 days thereafter showed no decrease in cholinesterase (Rider *et al*., 1972).

B. Observations in Other Species

Acute Effects. Both disulfoton and phorate have high acute toxicity in laboratory animals. The oral LD_{50} of phorate in rats is reported variously as 1.75 mg/kg (Hazleton, 1953); 2.71 mg/kg, 3.66 mg/kg, and 4.11 mg/kg (Tusing, 1955); and 17.7 mg/kg (American Cyanamid, 1966, Cited in USEPA, 1974e). The oral LD_{50} of disulfoton in male rats is reported variously as 12.5 mg/kg (Bombinski and DuBois, 1958; Wysocka-Paruszewska, 1970) and 6.8 mg/kg (Gaines, 1969) and in female rats as 2.6 mg/kg (Wysocka-Paruszewska, 1970; Bombinski and DuBois, 1958), 2.3 mg/kg (Gaines, 1969), and 2.8 mg/kg (McPhillips and Dar, 1967). Studies on the acute oral toxicity of phorate in other animals were not found. The acute oral LD_{50} of disulfoton in mice and guinea pigs are about the same as those in rats (Bombinski and DuBois, 1958; Stevens *et al*., 1972).

Studies to determine the acute dermal LD_{50} of phorate gave values of 3 mg/kg in rats (Shaffer, 1958), 20 mg/kg in male guinea pigs (American Cyanamid, 1966, Cited in USEPA, 1974e), and 71 mg/kg in rabbits (American Cyanamid, 1966, Cited in USEPA, 1974e). The acute dermal LD_{50} values of disulfoton are 6.0 mg/kg in females and 15.0 mg/kg in male rats (Gaines, 1969). The oxidative metabolites of phorate and disulfoton are at least as toxic as the parent compounds. Although specific information is not available in the open literature, the same toxicity relationships hold for disulfoton and its oxidative metabolites.

Subchonic and Chronic Effects. Subchronic feeding studies have been carried out with phorate and its oxidative metabolites. Four groups of 10 male Carworth Farms rats were given 88% technical phorate in the diet at 1, 5, and 25 ppm for 28 days. Cholinesterase in the 1-ppm group was not decreased (Tusing, 1955). In a second rat study, the no-adverse-effect dosage was

0.66 ppm. Groups of 50 male and female rats each were fed 93% phorate for 13 weeks at 0.22, 0.66, 2.0, 6.0, 12.0, and 18.0 ppm (Tusing, 1956).

Groups of three dogs (two females and one male) received 92% phorate at 0.01, 0.05, 0.25, and 1.25 mg/kg 6 days/week for 13-15 weeks. The no-adverse-effect dosage was judged to be 0.01 mg/kg, although very slight decrease in plasma cholinesterase did result even then. Higher dosages caused significant depression of cholinesterase and mortality at the two highest dosages (Tusing, 1956).

Rat feeding studies showed higher subchronic toxicities on phorate oxidative metabolites (Bombinski et al., 1958).

Studies of the subchronic toxicity of disulfoton have measured cholinesterase decrease in animals and the effect of repeated administration of the compound on their tolerance of it. However, none of these studies were designed to allow the extrapolation of a no-adverse-effect dosage of disulfoton based on cholinesterase decrease. There are no reports of long-term chronic feeding studies of either phorate or disulfoton.

Mutagenicity. No available data.

Carcinogenicity. No chronic feeding studies of phorate or disulfoton in which carcinogenicity could be evaluated have been reported.

Reproduction. CFI mice from Carworth Farms were fed diets containing 98.7% phorate at 0.6, 1.5, and 3.0 ppm. Pups were weaned directly onto diets that were being fed to the parents for a three-generations reproduction study. Reproductive performance and lactation were evaluated. In addition, a rather complete series of pathology evaluations was done to establish that the no-adverse-effect level for reproductive performance was 1.5 ppm (American Cyanamid, 1965b, cited in USEPA, 1974e).

There are no published studies on the effects of disulfoton on reproduction.

Teratogenicity. No teratogenicity studies of phorate have been reported. However, in the studies on reproductive performance reported above, no abnormalities, including skeletal changes, could be related to phorate administration. Phorate was also studied in the chick embryo test (Richert and Prahlad, 1972). Phorate in peanut oil was injected into eggs on the tenth day of incubation at 1.5 or 2.0 ppm. Controls received peanut oil only. Hatchability of the eggs was decreased in a dose-dependent manner. Malformations were produced, but these did not seem to be dose-related. The relevance of these studies to mammalian teratology is unclear.

There are no published reports of teratogenicity studies of disulfoton.

IV. CONCLUSIONS AND RECOMMENDATIONS

Phorate and disulfoton are widely used agricultural insecticides. They are organophosphorus compounds whose mode of action, inhibition of acetylcholinesterase, is well understood. Both have high acute toxicity in laboratory animals. Because of this and a known mode of action, studies on the possible chronic toxicity of these compounds have been neglected. There is very little toxicologic research on disulfoton reported in the open literature. There is a single subchronic-toxicity study, in which no adverse effects were observed after administration of 0.75 mg/kg/day for 30 days; this indicates that disulfoton would pose less hazard than phorate. Based on subchronic toxicity data an ADI was calculated at 0.0001 mg/kg/day for both phorate and disulfoton. The available data and calculations of ADI are summarized in Table VI-31.

Phorate and disulfoton are converted in the environment and in mammalian systems to a series of highly toxic oxidative metabolites, which are known to be more potent cholinesterase inhibitors than the parent compounds (Curry *et al.*, 1961). These materials must be considered when evaluating the toxicity of phorate and disulfoton. Therefore, it is proposed that the derived no-adverse effect dosages of these compounds be considered to include their oxidative metabolites as well.

Sensitive methods for analyzing residues of phorate and disulfoton are available. A gas-liquid-chromatographic method is available that can detect 0.01 ppm in milk; and a cholinesterase-inhibition method can detect as little as 0.008 ppm in a 5-g crop sample. However, it is clear that the analytic methods available will be barely adequate for the analysis of these materials in drinking water. Particular care will have to be taken to ensure that sample sizes are great enough to allow detection of concentrations as low as 0.0007 ppm.

The most obvious research need for both these compounds is studies on chronic toxicity, including carcinogenicity and teratogenicity. Some of these studies may have been done by the manufacturers; if so, they should be made generally available to assist in the evaluation of toxicology by the scientific community.

There is also a need for corroboration of the no-adverse effect cholinesterase-inhibition dosage in human subjects in a controlled study with at least two dosages. This would allow the extrapolation of a no-adverse-effect dosage with a higher degree of confidence and a lower uncertainty factor.

TABLE VI-11: Summary of Chronic Toxicity Data for Phorate

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Rats	28 days	1-25 ppm in diet, 10 animals per group	1ppm	no adverse effect	Tusing, 1955
Rats	13 weeks	0-18 ppm in diet, 100 animals per group	0.66 ppm	no adverse effect	Tusing, 1956
Dogs	13-15 weeks	0-1.25 mg/kg/day in diet, 3 animals per group	0.01 mg/kg/day[c]	slight cholinesterase depression	Tusing, 1956
Rats	13 weeks	0-3 ppm in diet, 100 animals per group	0.32 ppm	no adverse effect	Amer. Cyanamid, 1966a, 1966b

Using an uncertainty factor of 100, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{0.01}{100} = 0.0001 \text{ mg/kg/day(Adult)}, \quad 0.0001 \times 70^{a} \times 0.1^{b} = 0.0007 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Test study from which to calculate suggested no-adverse-effect level.

MALATHION

1. INTRODUCTION

Malathion, or *S*-1,2-*bis*(ethoxycarbonyl)ethyl-*O*,*O*-dimethylphosphorodithioate, is a wide spectrum, extensively-used organophosphorus insecticide. Agricultural, home, and garden uses of malathion accounted for about two-thirds of the domestic use in 1972. The remaining one-third of malathion use was for industrial, commercial, and governmental purposes. Malathion was one of the earliest organophosphorus compounds to be developed as an insecticide and is registered for use on more than 130 crops against a wide spectrum of insects and mites.

Use of malathion in 1971 is estimated to have been approximately 3.6 million pounds (National Academy of Sciences, 1975). This amount represented approximately 2% of the total insecticide use in the United States that year. This was a smaller amount than reports indicated for 1964 and 1966, when the use was approximately 5 million pounds. It has been estimated that the use of malathion has increased since 1971 (USEPA, 1976a). The total quantity used in agriculture was distributed fairly evenly throughout all geographic regions of the United States, except for the northeastern states, where somewhat smaller amounts were used.

The production of malathion involves a two-step process: first, *O*,*O*-dimethyldithiophosphoric acid is prepared by the reaction of methanol and phosphorus pentasulfide; the acid then reacts with diethylmaleate or diethylfumarate to produce malathion. The currently used process yields 95% malathion. Malathion is soluble in water at approximately 145 ppm at 25°C. The stability of malathion in solution is a function of pH (Spiller, 1961). Its half-life at a pH of 9.0 is 12, whereas it was hydrolysed instantaneously at a pH of 12.0. No hydrolysis took place in 12 days in solutions at a pH of 5.0 - 7.0. Conrad *et al.* (1969) found no degradation in 7 days at a pH of 2.0, 4.0, or 6.0.

In studies of the persistence of malathion in water, it was determined that the half-life in raw river water was less than 1 week, whereas malathion remained stable in distilled water for 3 weeks (Eichelberger and Lichtenberg, 1971). This difference may result from biologic activity in the raw river water. These results are confirmed by studies conducted in Czechoslovakia in which malathion at a concentration of 10 ppm degraded almost completely within 10 days in "environmental water" (Jirk *et al.*, 1971). Lewis and Eddy (1959) applied malathion at 1, 3, and 6 pounds/acre to log ponds in Oregon for the control of mosquito larvae. Under these conditions, malathion was effective for 2.5-

6 weeks. In studies in the Virgin Islands, where malathion is extensively used for insect control, only 2 of 49 water samples taken from cisterns contained malathion, and there the concentrations were extremely low. However, a malathion metabolite that was not identified was present in all samples (Lenon *et al.*, 1972). In general, malathion is degraded in water more rapidly than other organophosphorus insecticides under the same conditions. However, the question of the production of metabolites and their persistence in water is largely uninvestigated.

Malathion tolerances ranging from 0.1 to 8 ppm on food crops and as high as 135 ppm on forage crops have been established in the United States for 127 raw agricultural commodities. The tolerances of malathion on most food crops are 8 ppm. The WHO/FAO has established the acceptable daily intake of malathion at 0.02 mg/kg. Market Basket Surveys conducted by the FDA revealed that most of the organophosphorus-insecticide residues in food are malathion. The 4-year average (1965-1969) malathion concentration was 0.00013 ppm, whereas the total organophosphate residues were 0.00017 ppm (Duggan *et al.*, 1971). The largest residues were present in grain and cereal products. None of the residue concentrations found in the Market Basket Surveys exceeded the acceptable daily intake of malathion.

II. METABOLISM

After ingestion by mammals, malathion is rapidly absorbed from the digestive system. Distribution then is general, and very low concentrations of malathion are found in many tissues. The concentrations in liver and bone are generally somewhat higher than those in other tissues (March *et al.*, 1956).

Malathion is a phosphorodithioate insecticide and thus requires activation to the phosphate, if it is to become an active anticholinesterase agent (Metcalf and March, 1953). It has been shown that the conversion of malathion to malaoxon is a reaction carried out by the liver microsomal monooxygenase system (O'Brien, 1957). Competing with the activation of malathion are enzymes responsible for its degradation to nontoxic metabolites. These are generally characterized as phosphatases and carboxylesterases or aliesterases. Products of reactions catalyzed by these enzymes are malathion monoester, various phosphoric acids, and the demethylated product (Krueger and O'Brien, 1959; Cohen and Murphy, 1972; Cook and Yip, 1958). However, it has been shown that the degradation rate of malaoxon exceeds the activation rate of malathion, so there is generally little accumulation of the toxic activation product in mammalian systems (Dahm *et al.*, 1962).

The toxicity of malathion is potentiated by O-ethyl O-para-nitrophenyl phenylphosphonothioate, tri-o-tolylphosphate, and some other organophosphorus compounds. It is postulated that this potentiation results from the inhibition of carboxylesterase or aliesterase enzymes responsible for degradation of malathion in mammals. Presumably, this mechanism would lead to increased formation of malaoxon, the activation product, because the enzymes responsible for degradation of malaoxon would be inhibited (DuBois, 1972).

III. HEALTH ASPECTS

A. Observations in Man

Studies with human volunteers have resulted in the conclusion that up to 16 mg of malathion may be ingested daily for up to 47 days with no significant effect on plasma or red-cell cholinesterase activity. One group of five volunteers was fed 16 mg of malathion daily for 88 days (Rider *et al.*, 1959). During the last 41 days of the treatment, the subjects also received 3 mg of EPN. In a separate study (Moeller and Rider, 1962) 8, 16 and 24 mg/day per person for 47 days yielded the conclusion that the threshold of toxicity appeared to be 24 mg/day. Smaller amounts had no adverse effect in human subjects.

There are many recorded cases of malathion poisoning in humans, including many attempted suicides. These reports lead to the conclusion that relatively large quantities of malathion can be ingested by humans without mortality if proper therapy is applied after ingestion. Subjects who have ingested as much as 60 g have survived. However, as little as 5 g has resulted in mortality in some adults.

B. Observations in Other Species

Acute Effects. The acute oral LD_{50} of malathion is 480-2,100 mg/kg in male and 739-1,000 mg/kg in female rats, depending on the vehicle of administration and the purity of the malathion (Hazleton and Holland, 1953; Frawley *et al.*, 1957; Kimmerle and Lorke, 1968; Gaines, 1969).

Mice appear to be less susceptible to malathion poisoning than rats, with males and females being about equally susceptible. LD_{50} values range between 720 mg/kg for 90% technical malathion and 3,320 mg/kg for 99% pure material (Hazleton and Holland, 1953; Golz and Shaffer, 1956). The acute oral LD_{50} is 570 mg/kg in guinea pigs (Hagan, 1953) and greater than 900 mg/kg in rabbits (Aukins *et al.*, 1955).

Acute toxicity by routes of administration other than oral is also relatively low. In rats, the intraperitoneal LD_{50} is 750 mg/kg (Kimmerle and Lorke, 1968; Brodeur and DuBois 1963), the subcutaneous LD_{50} is 1,000 mg/kg (Spiller, 1961), and the dermal LD_{50} is greater than 4,444 mg/kg (Gaines, 1969). The intraperitoneal LD_{50} of malathion in mice is reported to be 420-474 mg/kg (Hazleton and Holland, 1953) and 815 mg/kg (O'Brien et al., 1958). The intraperitoneal LD_{50} in guinea pigs is 500 mg/kg (Spiller, 1961). The acute intraperitoneal LD_{50} of a 19% solution of malathion in dogs is reported to be 1.51 ml/kg (Guiti and Sadeghi, 1969).

Subchronic and Chronic Effects. Subchronic oral toxicity studies of malathion in rats have been conducted for periods of 33 days (Golz and Shaffer, 1956), 8 weeks (Frawley et al., 1957), 5 months (Kalow and Marton, 1961), and 6 months (Holland et al., 1952). Malathion concentrations in these studies ranged from 100 to 5,000 ppm. At no dose in any study was there an evident effect on food intake, weight gain, or growth. At 100 ppm, no effects were observed, even on red-cell cholinesterase activity. In two studies, 500 ppm for 8 weeks also produced no adverse effect on whole-blood cholinesterase activity. At 1,000 ppm and higher, however, red-cell cholinesterase activity was significantly decreased.

Intraperitoneal injection of malathion in rats for 60 days resulted in a no-adverse-effect level of 100 mg/kg without mortality, but dosages of 200 and 300 mg/kg resulted in mortality rates of 60 and 100%, respectively (DuBois et al., 1953).

Other studies on the subchronic toxicity of malathion with other experimental animals did not result in data that could be used to project a no-adverse-effect dosage of malathion or that would be useful in evaluating its toxicity and hazard in drinking water.

Two studies on the chronic toxicity of malathion in rats have been reported. Hazleton and Holland (1953) fed malathion at 100, 1,000, and 5,000 ppm as the 65% technical material in 25% wettable powder. There was no mortality during the 2-year test period, and no gross effects were observed at 100 and 1,000 ppm. At 5,000 ppm, food intake and weight gain were reduced. Significant decreases in plasma, red-cell, and brain cholinesterase were observed at 1,000 and 5,000 ppm, but not at 100 ppm. Hazleton and Holland also fed technical 90% malathion as a 25% wettable powder at the same dosages for 2 years. Growth rate and food intake were not influenced, but a significant decrease in cholinesterase activity was observed at all dosages.

Golz and Shaffer (1956) administered 99% malathion as a 25% wettable powder in the diet of rats at 500, 1,000, 5,000, and 20,000 ppm for 2 years. A significant decrease in red-cell cholinesterase activity was observed at all dosages. Reductions in growth and food intake were observed at 20,000 ppm. In view of the chronic feeding studies with rats, the WHO/FAO has established the no-effect concentration of malathion at 100 ppm (WHO/FAO, 1965).

Surprisingly, the only other chronic studies of malathion toxicity found in the literature involved chickens. Malathion at 250 and 2,500 ppm in the diet of male and female chickens for 2 years produced no adverse effect on hatchability. At the higher dosage, plasma cholinesterase activity was decreased (WHO/FAO, 1965). Chickens fed for 15 weeks at 10,000 ppm all died (Frawley et al., 1956).

Mutagenicity. No information on the possible mutagenic effects of malathion was found in the literature.

Carcinogenicity. No information on the possible oncogenic effects of malathion was found in the literature.

Reproduction. In the studies of Kalow and Marton (1961), in which rats were fed malathion at 4,000 ppm in the diet, significant effects on reproduction were observed. The numbers of newborn rats that were alive at 7 days were 105 for controls and 56 for the treated animals. At weaning in 21 days, there were 75 live controls and 34 live treated animals. At 9 weeks after birth the average body weight of the treated group was significantly lower than that of the controls.

When malathion was injected into hen eggs at 25, 100, 200, 300, 400, and 500 ppm in acetone, the hatchability of the eggs was reduced to 85, 87, 62, 71, 42, and 6%, respectively. When malathion in corn oil was injected at 50, 100, and 200 ppm, hatchability was reduced to 84, 9, and 9% (Dunachie and Fletcher, 1969). Studies by other authors have confirmed the reduced hatchability of chicken malathion injection.

Teratogenicity. No teratogenic effects were observed when rats were treated intraperitoneally with malathion at 900 mg/kg. This dosage was determined in preliminary studies to be the highest nonfatal dosage. On day 11 after insemination, pregnant rats were given a single intraperitoneal injection of malathion. No significant difference between treated females and controls relative to dead fetuses per litter, resorptions, average weight of fetuses, average weight of placenta, or fetal malformations were observed (Kimbrough and Gaines, 1968). The authors suggested that feeding studies would have been a more practical and significant approach to the study of teratogenic effects of malathion.

A variety of different studies have been conducted with malathion in the avian egg embryotoxicity assay. When malathion was injected on day 4 at 1 mg/egg, no teratogenic signs were detectable. The length of embryo parts indicated no difference between malathion eggs and controls. Embryonic cholinesterase was also not decreased (Upshall et al., 1968). Roger et al. (1969) reported that malathion injected into the egg at 1 mg reduced hatchability to 70%, compared with control hatchability of 95%. Again, there was no indication of teratogenic effects.

IV. CONCLUSIONS AND RECOMMENDATIONS

Malathion is a widely used organophosphorus insecticide with a wide spectrum of activity and many diverse uses in agricultural, home, and garden applications. It is quite likely that malathion could appear as a contaminant of drinking water, although there are no reports of its having been found as yet. The mode of action of malathion is similar to that of other organophosphorus insecticides--inhibition of acetylcholinesterase. Its acute toxicity, however, is quite low, compared with that of other members of this class of insecticides, primarily because of its facile metabolism in mammalian systems, by carboxylesterase or aliesterase enzymes, to products of decreased or no toxicity. Its toxic potential, however, is illustrated by the possibility of potentiation when degradative enzymes are inhibited by other chemicals.

The chronic-toxicity information available in malathion is surprisingly sparse for a compound that has been so extensively used in the past. However, the two rat studies that have been reported, the subchronic administration of malathion to human volunteers, and the establishment of no-adverse-effect dosages in rats and humans on the basis of anticholinesterase activity allows the establishment of a no-adverse-effect concentration for drinking water with a high degree of assurance of safety. An ADI was calculated at 0.02 mg/kg/day based on these data. The available toxicity data and calculations of ADI are summarized in Table VI-32.

Additional chronic toxicity data are needed for malathion, with particular concentration on long-term feeding studies in which teratogenicity, mutagenicity, and carcinogenicity are evaluated. Of particular importance would be a good study of the metabolism and persistence of malathion in water. In view of the extent of past use of malathion, continued monitoring for its presence in food materials and water is necessary.

TABLE VI-32. Summary of Toxicity Data for Malathion

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-Adverse-Effect Level or Lowest Minimal-Effect Level	Effect Measured	Reference
Rat	77 days	0, 100, 1,000, 5,000 ppm in diet	100 ppm (5 mg/kg/day)[d]	Depression of erythrocyte cholinesterase	Golz and Shaffer, 1956
Rat	8 weeks	0, 100, 500 ppm in diet	100 ppm (5 mg/kg/day)[d]	Depression of whole blood cholinesterase	Frawley et al., 1957
Rat	6 months	0, 5,000 ppm in diet	-----	Normal growth	Kalow and Marton, 1961
Rat	6 months	0, 1,000 ppm in diet	1,000 ppm (50 mg/kg/day)[d]	No adverse effects	Holland et al., 1952
Rat	60 days	0, 100, 200, 300 mg/kg/day i.p. injection	100 mg/kg/day	No mortality	DuBois et al., 1953
Rat	2 years	0, 100, 1,000, 5,000 ppm of tech. 95% malathion	100 ppm (5 mg/kg/day)[d]	Depression of cholinesterase	Hazleton and Holland, 1953
Rat	2 years	0, 100, 1,000, 5,000 ppm of tech. 95% malathion	none	Depression of cholinesterase	Hazleton and Holland, 1953
Rat	2 years	0, 500, 1,000, 5,000 20,000 ppm tech. 95% malathion	none	Depression of cholinesterase	Golz and Shaffer, 1956
Man	47 days	0, 8, 16, 24 mg per day	16 mg/day (0.23 mg/kg/day)[a,c]	Depression of cholinesterase	Moeller and Rider, 1962

Using an uncertainty factor of 10, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{0.23}{10} = 0.023 \text{ mg/kg/day (ADI)};\ 0.023 \times 70^{a} \times 0.2^{b} = 0.16 \text{ mg/liter}.$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters; and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse-effect level.

[d] Assume weight of rat = 0.4 kg and average daily food consumption of rat = 0.02 kg.

PARATHION AND METHYL PARATHION

I. INTRODUCTION

Parathion, or (O,-O-diethyl-O-p-nitrophenylphosphorothioate, and methyl parathion, or O,O-dimethyl-O-p-nitrophenylphosphorothioate, are closely related, highly toxic organophosphorus insecticides. Both have a wide spectrum of activity against insects and some mites, and both are registered for use on a large number of crops, including field, forage, and vegetable crops. Essentially all domestic use of both parathion and methyl parathion is in agriculture. Use of these compounds is concentrated in the south central states, with smaller amounts used in the Southwest and Southeast, and much smaller amounts used in other regions of the country.

The EPA estimates that 51 million pounds of methyl parathion and 14 million pounds of parathion were produced in 1973 in the United States (USEPA, 1975g,h). Domestic use that year is estimated at 40 million pounds of methyl parathion and 10 million pounds of parathion. In 1971, parathion and methyl parathion together accounted for more than 22% of all insecticide used in the United States (NAS, 1975). The current figure is undoubtedly higher, because the prohibition of DDT has changed patterns of use of insecticides.

Parathion and methyl parathion are prepared by the reaction of diethyl or dimethyl phosphorothionochloridate with sodium p-nitrophenate. The chemical properties of the resulting insecticides are quite similar. Both are readily oxidized in air to the corresponding oxygen analogue (oxon), which is the toxic form of the material. Hydrolysis of the compounds virtually destroys insecticidal activity. Methyl parathion is hydrolyzed considerably faster than parathion in water (USEPA, 1975h). Parathion is soluble in water at 24 ppm at 25°C, and methyl parathion, at 55 - 60 ppm at 25°C (USEPA, 1975g,h).

Relatively little information is available on the persistence and fate of parathion and methyl parathion residues in water, especially under field conditions (Paris and Lewis, 1973). In general, parathion has been shown to be 2 - 3 times more persistent than methyl parathion in natural water systems. Although no specific data are available on the possible bioaccumulation or biomagnification of parathion and methyl parathion, their physical, chemical, and biological properties make it unlikely that these phenomena will occur in food chains or food webs.

The acceptable daily intake of parathion has been established at 0.0005 mg/kg (FAO/WHO, 1968), and of methyl parathion, 0.001

mg/kg (FAO/WHO, 1969). The residues of both compounds that have been found in the various Market Basket Surveys and similar studies have been well below the acceptable daily intakes established by the FAO/WHO. Neither substance has been identified in drinking water in the United States.

II. METABOLISM

The metabolism of both parathion and methyl parathion has been extensively studied in a wide variety of organisms, including microorganisms, plants, insects, and mammals. Both compounds depend on oxidative activation by replacement of the thiono sulfur with oxygen for their toxicity. Competing with this intoxication reaction are hydrolysis reactions that result in detoxification. The ring nitro group can also be reduced, particularly in bovine rumen fluid, to an amino group; this results in amino parathion, whose toxicity is much lower.

These compounds are readily absorbed through the skin of animals exposed to their residues. They are rapidly transported throughout the system after absorption. Oxidative activation takes place primarily in the liver. A number of workers have shown that in liver microsomal mixed-function oxidase systems that the presence of reduced nicotinamide adenine dinucleotide phosphate and oxygen are responsible for this reaction. The conversion of parathion to paraoxon has been demonstrated both *in vivo* and *in vitro*.

Degradative reactions that result in detoxification of parathion and methyl parathion involve either demethylation or dearylation. The resulting desmethyl compounds and dimethyl phosphoric acids are essentially nontoxic. Urinary excretion of p-nitrophenol resulting from dearylation has been used as a test for parathion poisoning.

The only tissue accumulation of parathion or methyl parathion that has been observed is the irreversible binding to esterase enzymes. The highest concentrations are in the liver and lung.

III. HEALTH ASPECTS

A. Observations in Man

The fatal dosage of parathion in man has been estimated at 1.43 mg/kg in one report (DuBois, 1958), and 2.0 mg/kg in another (Hayes, 1967). No information has been found on the lethal dosage of methyl parathion in man.

There are many literature citations of acute and subacute poisoning of humans by parathion, usually presented as individual case studies of accidental poisoning. Most of these reports do not lend themselves to calculations of LD_{50} or the establishment of no-adverse-effect dosages. There are, however, two studies that allow the establishment of a no-adverse effect dosage of parathion in man. Edson *et al.* (1964) established that ingestion at 0.05 mg/kg/day in the diet for 42 days produced no decrease in red-cell cholinesterase; 0.1 mg/kg/day did significantly reduce both plasma cholinesterase and red-cell cholinesterase. In another experiment (Rider *et al.*, 1969), prison volunteers were fed parathion at 3.0, 4.5, 6.0, and 7.5 mg/day. Assuming the average weight of a human adult to be 70 kg, these dosages would result in the ingestion of 0.043, 0.064, 0.086, and 0.11 mg/kg/day. At the highest dosage, plasma cholinesterase was decreased in one subject on day 4 and in all subjects by day 16; the decrease was to 29% of the control value. The three lower dosages resulted only in a slight decrease in plasma cholinesterase.

In the same series of studies, methyl parathion at dosages as high as 19 mg/day (0.27 mg/kg/day) for 4 weeks produced no significant change in plasma or red-cell cholinesterase.

B. Observations in Other Species

Acute Effects. Both parathion and methyl parathion are among the most toxic of the organophosphorus insecticides. Acute oral LD_{50} values have been determined for a number of laboratory animals and other species. The oral LD_{50} of parathion ranges between 2 and 30 mg/kg in male and 1.75 to 6 mg/kg in female rats; the mean LD_{50} is 7.6 mg/kg in males and 3.5 mg/kg in females (USEPA, 1975h). Methyl parathion is somewhat less toxic. The oral LD_{50} is 5.8 - 16 mg/kg in male and 4.5 - 24 mg/kg in female rats; the means are 11.1 and 16.5 mg/kg (USEPA, 1975g).

The acute oral toxicity of parathion averages 23.0 mg/kg in male mice and 12.7 mg/kg in a mixed population (USEPA, 1975h). The acute oral toxicity of methyl parathion averages 18.5 mg/kg in mice (USEPA, 1975g). LD_{50} values of parathion in other animals are about the same as in rats and mice. LD_{50} values of 9.3 - 32.0 mg/kg in guinea pigs have been reported. In rabbits, 68 mg/kg has been reported. Toxicity of methyl parathion in guinea pigs and rabbits is lower than that in rats and mice. The LD_{50} is 417 mg/kg in guinea pigs and, according to two reports, 420 and 1,270 mg/kg in rabbits..

The high toxicity of parathion and methyl parathion is also reflected in the LD_{50} values determined by routes other than oral. The intraperitoneal LD_{50} of parathion ranges from 1.6 - 7 mg/kg in male rats and is 4 mg/kg in female rats. The dermal LD_{50} is about 21 mg/kg in male and 6.8 - 100 mg/kg in female rats. Inhalation toxicity is 0.0315 mg/liter for 4 h and 0.115 mg/liter for 1 h. The intraperitoneal LD_{50} of methyl parathion is 3.5 mg/kg, the dermal LD_{50} is 67 mg/kg, and inhalation toxicity is 0.2 mg/liter for 1 h in rats. The data reported for other animals for both parathion and methyl parathion are similar to those reported for rats.

Acute poisoning from parathion and methyl parathion is related to their inhibiting action on the enzyme acetylcholinesterase. Toxic manifestations generally occur only after more than 50% of the plasma cholinesterase is inhibited. If an animal survives acute poisoning, it takes about 4 weeks for plasma cholinesterase to return to normal.

Subchronic and Chronic Effects. Edson and Noakes (1960) fed diets containing parathion to rats for 15 and 16 weeks, after which the survivors were sacrificed and examined. Feeding at 15.4 mg/kg/day (125 ppm in the diet) resulted in death of three of the 10 rats in the group. No mortality occurred at 2.4 mg/kg/day (25 ppm) or 0.52 mg/kg/day (5 ppm).

Edson et al. (1964) determined the no-adverse effect dosage of parathion in rats to be 0.02 mg/kg/day when the compound was fed over an 84 day period. A minimal effect was found at 0.04 and 0.06 mg/kg/day. The criterion of effect was decreased in plasma cholinesterase activity.

The subchronic toxicity of parathion in dogs was studied by Frawley and Fuyat (1957). Parathion was incorporated into the diet of dogs at 1, 2, and 5 ppm, and animals were fed for 24 weeks. At 1 ppm (average, 0.021 mg/kg/day) a minimal but significant reduction in plasma cholinesterase occurred. At the higher dosages (2 ppm, or 0.047 mg/kg/day; 5 ppm, or 0.117 mg/kg/day), plasma cholinesterase was reduced by 60 - 70%. Hazleton and Holland (1950) gave 15% parathion wettable powder in gelatin capsules to dogs 6 days/week for 90 days. At 3 mg/kg/day, the dogs lived 3 weeks but exhibited toxic signs continuously. At 1 and 2 mg/kg/day, the animals survived the test period, but were nervous and irritable during the early stages of treatment; later, their behavior seemed normal. No gross pathology was evident, but histopathologic examination after termination of the experiment revealed degenerative changes in the liver.

Subchronic toxicity in other domestic animals has been reported. Oral doses as low as 8 mg/kg given daily were lethal to a goat in 11 days. Other subchronic doses resulting in mortality ranged from 12 mg/kg for 5 days to 32 mg/kg for 10 days (Wilber et al., 1955). In sheep, the maximal safe oral dose has been determined to be 10 mg/kg (Radeleff, 1958). In cattle, parathion given by capsule at 0.022 and 0.112 mg/kg/day for 81 days produced no noticeable adverse effects. In another study, 0.11 and 0.89 mg/kg/day had no adverse effects (Fahm et al., 1950).

Subchronic-toxicity studies of methyl parathion are lacking for rats, mice, and guinea pigs. The only report of a subchronic-toxicity study of methyl parathion was reported by the FAO/WHO in 1969. A 12-week feeding study at 5, 20, and 50 ppm was conducted with dogs. Assuming that the dogs weighed 10 kg and consumed 200 g/day, the dosages were 0.1, 0.4, and 1.0 mg/kg/day. Significant decrease in plasma cholinesterase activity was observed at 50 ppm; no significant decrease was observed at 5 ppm; and decrease was questionable at 20 ppm.

Hazleton and Holland (1950) fed male rats for 104 weeks and female rats for 64 weeks parathion at 10, 25, 50, and 100 ppm in the diet. Mortality was 40% in male controls and 33% in female controls. Mortality in the test groups was not higher than that in the controls, even at the highest dosage. At 100 ppm, female rats did exhibit some evidence of toxicity. All females in the control and 10-ppm groups produced living litters. All but one female in the 50-ppm group bore living litters. No other chronic-toxicity studies of parathion or methyl parathion have been reported.

A three-generation study of methyl parathion in rats (USEPA, 1975g) at 10 and 30 ppm showed no consistent effect in number of live or dead births, physical structure of newborn, litter size, weanling weights, or percentage survival to weaning. At the higher dosage, there was decreased reproductive performance in some instances. This was not apparent at 10 ppm, which approximates 0.5 mg/kg/day. A comparable study has not been reported for parathion.

A number of studies in avian species have indicated that effects of both parathion and methyl parathion are minimal. Shellenberger et al. (1966) reported that egg production in Japanese quail was inhibited and hatchability was reduced by methyl parathion at 60 ppm and parathion at 27 ppm. Mueller and Lochman (1972) fed subtoxic doses of parathion to yearling mallards to observe effects on egg production, fertility, hatchability, shell thickness, and progeny growth. The mallards were fed parathion at 10 ppm in the diet beginning 30 days before egg production and continuing for 90 days afterwards. Parathion had no adverse effect, except a reduction in mean shell thickness. Neill et al. (1971) reported a similar study with gray partridge that received parathion at 8 ppm. There was no adverse effect on egg production, fertility, and hatchability.

Mutagenicity. The *in vivo* effects of parathion on guinea pig chromosomes have been studied (Dikshith, 1973). Male guinea pigs were given 0.05 mg intertesticularly. The animals were killed after 24 h and examined for chromosomal changes at metaphase. Abnormalities were induced by the treatment, which confirmed that cell division is inhibited by parathion at metaphase.

The effect of methyl parathion on chromosomes of cells *in vivo* was studied with ICR male mice that received intraperitoneal injections (Huang, 1973). Dosage ranged from 5 to 100 mg/kg. Direct toxicity resulted from the two higher dosages, 50 and 100 mg/kg. At the lower dosages, as seen in examination of bone marrow, methyl parathion caused no increase in the incidence of chromosomal aberrations.

Carcinogenicity. There are no reports of oncogenic effects in experimental animals of either parathion or methyl parathion in long term feeding studies.

Teratogenicity. Methyl parathion has been studied in both rats and mice to ascertain teratogenic effects (Tanimura *et al.*, 1967). Animals received intraperitoneal injections on day 12 (rats) and day 10 (mice) of gestation at dosages approaching the LD_{50}. All animals exhibited some symptoms of toxicity. No significant external or internal malfunctions were observed in rats. However, some embryotoxicity was observed in mice at the highest dosage, 60 mg/kg. Because of this, the FAO/WHO has determined that a higher safety factor is necessary for methyl parathion. Another study (Fish, 1966) gave essentially similar results for methyl parathion and parathion. Some embryotoxicity was observed, but no specific teratogenic effects were noted.

V. CONCLUSIONS AND RECOMMENDATIONS

Parathion and methyl parathion are highly toxic organophosphorus insecticides that are widely used in commercial agriculture. Acute toxicity of both compounds is very high, but chronic toxicity does not appear to be a major consideration. The mode of action of these compounds is well known to be inhibition of acetylcholinesterase. Subchronic and chronic studies with the compounds have been primarily concerned, therefore, with measuring the decrease in cholinesterase enzymes as a result of oral treatment or incorporation in the diet of a variety of animals.

An ADI was calculated at 0.0043 mg/kg/day for both parathion and methyl parathion based on human data on parathion. The available toxicity data and calculation of the ADI are summarized in Table VI-35 and 36.

The obvious scarcity of data on the toxicity of methyl parathion indicates a pressing need for research. It appears that the assumption has been made that methyl parathion is toxicologically the same as parathion and that extrapolations have been made from parathion toxicology to methyl parathion. The data on teratogenic effects of methyl parathion, however, indicate that this is not an acceptable procedure in this case. Furthermore, in the last several years, methyl parathion has greatly surpassed parathion in total volume of use, making the need for specific data on methyl parathion even more pressing. The first priority in developing new information must be on the possibility of teratological effects of methyl parathion.

TABLE VI-18: Summary of Chronic Toxicity Data for Parathion

Species	Duration of Study	Dosage Levels and No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level	Effect Measured	Reference
Rat	16 weeks	5-125 ppm in diet	125 ppm	Mortality	Edson and Noakes, 1960
Rat	84 days		0.02 mg/kg/day	No adverse effect	Edson *et al.*, 1964
Dog	24 weeks	1-5 ppm in diet	1 ppm	Cholinesterase depression	Frawley and Fuyat, 1957
Dog	60 weeks	1-3 mg/kg/day, orally	1 mg/kg/day	Behavioral effects	Hazleton and Holland, 1950
Man	30-42 days		0.05 mg/kg/day		Edson *et al.*, 1964
			0.043 mg/kg/day[c]	Cholinesterase depression	Rider *et al.*, 1969

Using an uncertainty factor of 10, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{0.043}{10} = 0.0043 \text{ mg/kg/day (ADI)};\ 0.0043 \times 70^{a} \times 0.1^{b} = 0.03 \text{ mg/liter.}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Test study from which to calculate suggested no-adverse-effect level.

TABLE VI-16. Summary of Chronic

Toxicity Data for Methyl Parathion

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-Adverse-Effect Level or Lowest Minimal-Effect Level	Effect Measured	Reference
Man	4 wks		0.27 mg/kg/day	cholinesterase depression	Rider et al., 1969
Dog	12 wks		0.4 mg/kg/day	cholinesterase depression	FAO/WHO, 1969

Data are considered inadequate for calculation of ADI

J. CARBAMATES

ALDICARB AND METHOMYL

I. INTRODUCTION

Aldicarb [2-methyl-2-(methylthio)propionaldehyde O-(methyl carbamoyl)oxime] and methomyl [1-methylthioacetaldhyde O-(methylcarbamoyl)oxime] are two representatives of a class of carbamate insecticides known as "oxime carbamates". These materials are systemic insecticides with high toxicity to mammals. There are only a few registered uses for aldicarb on food crops, including potatoes, peanuts, and sugar beets; most of the use of this compound is on cotton. Methomyl, on the other hand, is a broad spectrum insecticide registered on several agricultural crops and commercially grown ornamental plants, for use primarily against lepidopterous insects on cole crops, tobacco, lettuce, cotton, and tomatoes.

Methomyl accounted for about 1% of the insecticides used by farmers on crops, livestock, and for other purposes in 1971 (National Academy of Sciences, 1975). 1.1 million pounds were used on crops. Although the amount of aldicarb used was less than 50,000 pounds in that year, the useage of this compound since then has probably increased. For methomyl, the principal use is in the Pacific states, which accound for over half of the total volume of application, followed by the Southeast, and then scattered use in other parts of the country. Aldicarb is not listed individually in the 1971 report and hence its use pattern is difficult to evaluate. However, it is estimated that most of its use is in the South central states and the Southwest where its use on cotton predominates. It is claimed that use of aldicarb has not reached a steady state and is expanding rapidly.

Both aldicarb and methomyl are synthesized by reacting the appropriate oxime with methyl isocyanate. Methomyl is produced by E.I. DuPont under the trademark Lannate and by Shell under the trademark Nudrin (Buchanan, 1971). The solubility of aldicarb in water is 0.6%, while methomyl dissolves to the extent of about 6%. Both compounds are very soluble in most organic solvents and both are quite stable in neutral or slightly acidic solutions. Generally, aldicarb persists in soil between 1 and 15 days. One does not expect to find residues of either aldicarb or methomyl in soil beyond the growing season during which it was applied.

Very little data on the behavior of aldicarb and methomyl in water are available. In a study of pond and lake water, half-lives of five days and six days were determined for aldicarb and methomyl (Moorefield, 1974).

Tolerances of aldicarb have been established on about 15 food and feed commodities. These tolerances range from 0.01 ppm in meat by-products to 1.0 ppm in potatoes and sugar beet tops. Methomyl is registered on a wide variety of forage crops, fruits, vegetables, cotton, and tobacco. Tolerances generally range between 0.1 ppm to 10 ppm. Acceptable daily intake levels have not been established for either aldicarb or methomyl. None of the available data in Market Basket Surveys conducted by the Food and Drug Administration indicate any residues of either aldicarb or methomyl in food. Neither compound is routinely included in the Market Basket analyses, however.

II. METABOLISM

As is the case with most carbamate insecticides, aldicarb is metabolized by both oxidative pathways and hydrolytic processes. Oxidation results in compounds which are also active cholinesterase inhibitors, while hydrolysis produces compounds of little or no insecticidal activity or toxicity to other organisms. Oxidation of aldicarb results in the sulfoxide and sulfone metabolites, both of which are active anticholinesterase agents (Bull *et al.*, 1967). Hydrolytic metabolites found include aldicarb oxime, the sulfoxide oxime, and sulfone oxime, indicating the importance of *N*-demethylation in the metabolism of the compound. Unidentified water soluble metabolites have also been reported by a number of workers (Andrawes *et al.*, 1967).

Aldicarb is readily absorbed from the gastrointestinal tract of treated animals. Excretion of the radiolabeled compound administered to rats is primarily in the urine, as approximately 80% appears within 24 hours, with an additional 1% in the feces. Only traces of the unchanged parent compound were found in the excreta. When aldicarb is labeled on the *N*-methyl carbon or the carbonyl carbon a large proportion of the radioactivity is found in the expired air as $^{14}CO2$ (Ryan, 1971). Very little aldicarb residues are found in the tissues or carcasses of treated animals.

In contrast to aldicarb, the metabolism of methomyl is primarily by the hydrolytic route. The principal metabolites found in the urine following treatment of rats with ^{14}C-labeled methomyl were the oxime-*O*-sulfate, the free oxime, the oxime glucuronide, and a trace of the parent compound. The absorption, excretion, and tissue distribution of methomyl follows a similar pattern to aldicarb. The expired air collected following the administration of methomyl to rats contained labeled CO_2 and acetonitrile (Knaak, 1971).

III. HEALTH ASPECTS

A. Observations in Man

In a single dose study three groups of 4 adult males each were given doses of aldicarb of 0.1, 0.05, and 0.025 mg/kg. At the high dose the subjects developed mild cholinergic symptoms. At the other doses there appeared to be a non-statistically significant cholinesterase depression, although by six hours after treatment cholinesterase levels in all subjects were normal. Inhibition of cholinesterase by aldicarb appears to be rapidly reversible (Union Carbide Corporation, no date, Cited in USEPA, 1975m).

Although aldicarb is an extremely toxic chemical, there have been relatively few cited examples of accidental poisoning. Furthermore, in cases of poisoning, the symptoms appear to be readily reversible and subjects who are poisoned normally recover within a short time, sometimes even a few hours (Heston, 1966).

Methomyl is a much newer insecticide and there are very few incidents of poisoning in man. There have been reports of occupational exposure poisonings resulting from methomyl when the compound was inhaled by workers in formulating plants. It is difficult, however, to evaluate such poisonings since workers who are occupationally exposed to methomyl are usually exposed to other organophosphorus insecticides as well. There have been no controlled studies of the occurrence of methomyl poisonings.

B. Observations in Other Species

Acute Effects. The acute toxicity of aldicarb is probably the highest of any widely used insecticide. The acute rat oral LD_{50} of aldicarb is reported to be 0.8 mg/kg for males and 0.65 mg/kg for females in studies using the technical grade compound suspended in peanut oil (Gaines, 1969). In corn oil the LD_{50} to rats was 0.9 mg/kg for males and 1.0 mg/kg for females (Weiden et al., 1965). The dermal toxicity of aldicarb is also high, as values of 3 mg/kg for males and 2.5 mg/kg for females were reported in 24 hour exposures of rats (Gaines, 1969).

The acute oral LD_{50} of aldicarb to the mouse was 0.3-0.5 mg/kg (Black et al., 1973). The dermal LD_{50} to rabbits was 4.96 mg/kg in 24 hour exposures (Weiden et al., 1965).

The rat oral LD_{50} values for methomyl fall in the range between 15 and 27 mg/kg (Felton, 1968; Neumeyer et al, 1969; Ben-Dyke et al., 1970). The LD_{50} values for oral administration of methomyl to mice were 28-49 mg/kg (Felton, 1968). These data were for technical methomyl in an unspecified solvent. The rat dermal LD_{50} of technical methomyl was greater than 1,000 mg/kg (Ben-Dyke et al., 1970).

Subchronic and Chronic Effects. Aldicarb was incorporated into the diet of CFE male and female rats in a 93 day study. Doses of 0.5, 0.1, 0.02, and 0 mg/kg/day were used. At the highest dose mortality was increased but not at the other levels. Survivors at all levels did not differ from controls with regard to pathology, organ weight, or plasma, erythrocyte, or brain cholinesterase levels. When aldicarb was fed at 1.2 mg/kg/day, the body weight of males and females was depressed. Both sexes experienced depression of plasma cholinesterase activity, whereas only the males experienced a depression of erythrocyte cholinesterase (Weil and Carpenter, 1969, Cited in USEPA, 1975m).

In an effort to ascertain whether tolerance was developed to aldicarb by multiple dosing, rats were treated at 0.5, 1.0, and 1.5 mg/kg with a 7 to 8 day interval between doses. No evidence of tolerance was observed since the LD_{50} values were approximately the same after the third dose as after the first. Similarly, no sensitizing properties were observed for aldicarb when guinea pigs were treated (Carpenter and Smyth, 1965; Possani and Kinead, 1968).

No subchronic studies using methomyl were found in the literature. A two year study of aldicarb in the diet of rats using dosage levels of 0, 0.1, 0.05, 0.025, and 0.005 mg/kg was conducted. Twenty males and 20 females were fed at each level. The following criteria of effect were measured: food consumption, mortality, life span, incidence of infection, liver and kidney weight as percentage of body weight, body weight gain, hematocrit, incidence of neoplasms, incidence of pathological lesions, and plasma, brain and erythrocyte cholinesterase levels. In no case did aldicarb-treated animals differ significantly from the controls for any of these parameters (Weil and Carpenter, 1965, Cited in USEPA, 1975m).

Weil also reported a two year feeding study in rats. Twenty animals of each sex were fed levels of 0.3 and 0.6 mg/kg/day of aldicarb sulfoxide, 0.6 and 2.4 mg/kg/day of aldicarb sulfone and mixtures of the two. No adverse effects were noted in the positive controls at 0.3 mg/kg/day of aldicarb, but the high dose of the sulfoxide/sulfone mixture caused increased mortality and plasma cholinesterase depression. Some increased mortality was observed in females at the high dose of the sulfoxide. No-adverse-effect levels in the two year study were estimated to be 0.3 mg/kg/day of aldicarb, 0.3 mg/kg/day of aldicarb sulfoxide, 2.4 mg/kg/day of aldicarb sulfone, and 0.6 mg/kg/day of a 1 to 1 mixture of sulfoxide/sulfone (Weil, Cited in USEPA, 1975m).

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Long term feeding studies of aldicarb in the diet of beagle dogs have been conducted. Four groups of 6 dogs each, 3 males and 3 females, were dosed at 0, 0.1, 0.05, and 0.025 mg/kg/day day for 2 years. Criteria of effect included body weight changes, appetite, mortality, histopathology, hematology, biochemistry, and terminal liver and kidney weights. No statistically measurable deleterious effects were found even at the highest dosage rate. The no-adverse effect level for dogs, therefore, was established as 0.1 mg/kg/day. This is the same as previously established for rats in two year and 90 day studies (Weil and Carpenter, 1966, Cited in USEPA, 1975m).

No chronic feeding studies using methomyl have been published.

Mutagenicity. The only mention of mutagenicity studies of aldicarb was in connection with the reproduction study reported above in which a dominant lethal test in rats showed no-adverse effects at 0.7 mg/kg (Weil and Carpenter, 1974, Cited in USEPA, 1975m). No studies of the mutagenicity of methomyl were found.

Reproduction. A three generation study has been conducted in which aldicarb was incorporated in the diet of a parent generation of rats 84 days before mating and into the diets of the subsequent generations at levels of 0.1 and 0.05 mg/kg/day. When the first generation offspring were 112 days old they were mated and their offspring collected and used as parents of F3 generation pups. The presence of aldicarb at either dose did not appear to affect the acceptability of the food of any generation. Evaluation of the effect of aldicarb on reproductive performance was made by comparing indices for fertility, gestation, viability, lactation, mean weight of male pups and female pups, micropathology on weanlings of the F3 generation and on 90 day adults of the F1 generation. In none of these measures were any statistically significant differences found between treated and control animals at either dose (Weil and Carpenter, 1964, Cited in USEPA, 1975m). A later report indicated aldicarb in the diet of rats at dosages up to 0.7 mg/kg/day had no effect on fertility, gestation, and survival (Weil and Carpenter, 1974, Cited in USEPA, 1975m).

A three generation reproduction study of methomyl was conducted in rats. Males and females were fed dietary levels of 50 and 100 ppm methomyl for three months after which the animals were mated. The F1 generation was continued on the diets for three months after which time they were bred to produce a second generation. The procedure was repeated for a third generation. Each generation was subjected to a complete histopathological examination and various other measures of the possible effect of methomyl on reproductive capacity were evaluated. No adverse effects upon reproduction were found at either feeding level (Bussey, 1968).

Teratogenicity. In an evaluation of the teratogenic potential of aldicarb in the diet of the rat (Weil and Carpenter, 1966, cited in USEPA, 1975m), no effect was found at dosages of 0, 0.04, 0.02, and 1.0 mg/kg. The highest dose level was close to the oral LD_{50} value but no significant effects were found on fertility, gestation, viability of pups, or lactation. No congenital malformations were found.

In studies using New Zealand white rabbits fed 0, 50, and 100 ppm of methomyl in the diet, no teratogenic effects were found in fetuses and pups after complete evaluations, including skeletal clearing and alizarin staining (Union Carbide Corporation, 1968, cited in USEPA, in preparation).

Carcinogenicity. Aldicarb was reported to be noncarcinogenic to mice (Weil and Carpenter, 1966, cited in USEPA, 1975m). C3H/HeJ male mice were painted with 0.125% aldicarb twice per week until the animals died. The incidence of tumors in this very susceptible strain was not significantly different from controls. No studies on the carcinogenicity of methomyl were found.

IV. CONCLUSIONS AND RECOMMENDATIONS

Aldicarb and methomyl are highly toxic, oxime-carbamate insecticides with increasing uses on food crops, cotton, and ornamentals. Both compounds act systemically and are readily metabolized and degraded in organisms and in the environment. It is not likely that either compound will appear as a major contaminant of drinking water. The mode of action of these materials is inhibition of acetylcholinesterase. Acute toxicity is quite high, but because of the rapid breakdown of the compounds in organisms and the environment, chronic toxicity is not a major problem.

The chronic toxicity data reported in the literature have not been sufficient as yet for WHO/FAO to establish an acceptable daily intake for either aldicarb or methomyl. An ADI of 0.001 mg/kg/day for aldicarb was calculated based on the available data. The available data on the chronic toxicity of aldicarb and calculations of ADI are summarized in Table VI-36.

In view of the relative paucity of data on the mutagenicity, carcinogenicity, and long term oral toxicity of Methomyl, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinkng water can be established. The behavior of either compound in water and the possibility of their appearing in drinking water is not understood and should be the subject of high priority research. Effects in humans have not been well-documented and efforts should be made in this direction.

TABLE VI-35: Summary of Toxicity Data for Aldicarb

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal Effect Level	Effect Measured	Reference
Rat	93 days	0-0.5 mg/kg/day	0.1 mg/kg/day	no adverse effects	Weil and Carpenter, 1968
Rat	2 years	0-0.1 mg/kg/day, 40 animals per group	0.1 mg/kg/day[c]	no adverse effects	Weil and Carpenter, 1965
Dog	2 years	0-0.1 mg/kg/day, 96 animals per group	0.1 mg/kg/day[c]	no adverse effects	Weil and Carpenter, 1966
Man	7 days	0.025-0.1 mg/kg/day, 4 animals per group	0.05 mg/kg/day	cholinesterase depression	Union Carbide Corp., no date

Using an uncertainty factor of 100, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{0.1}{100} = 0.001 \text{ mg/kg/day (ADI)}, \quad 0.001 \times 70^{a} \times 0.1^{b} = 0.007 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse-effect level.

CARBARYL

1. INTRODUCTION

Carbaryl, or 1-naphthyl-*N*-methylcarbamate, is a wide-spectrum carbamate insecticide effective against a variety of insect pests. The first registration was issued in 1959, and more than 1,200 products containing Carbaryl are now registered with the EPA. It is used agriculturally, in homes and gardens, on animals, and in forests. In 1971, 17.8 million pounds of carbaryl were used in the United States (National Academy of Sciences, 1975). This represents 10% of all insecticide used during that year and two-thirds of the total use of carbamate insecticides. The present use of carbaryl is undoubtedly greater, because it is one of the more useful substitutes for DDT.

Carbaryl is prepared in the United States by a commercial process involving the conversion of naphthalene by tetralin oxidation to 1-naphthol. Phosgene is prepared from chlorine and carbon monoxide and reacts with 1-naphthol in toluene solution to produce naphthyl chloroformate, which reacts with methylamine to yield 1-naphthyl-*N*-methylcarbamate, which crystallizes and is separated by centrifugation. The principal contaminant of the commercial process is 2-naphthy-*N*-methylcarbamate. The FAO provisional limit established for this impurity is 0.05%. The tetralin oxidation process produces a material well within this tolerance. This impurity is of concern, because it adversely affects crop flavor and may be cataractogenic (Fitzhugh and Bushka, 1949). Carbaryl is soluble in water at 40 ppm at 30°C. Hydrolysis of carbaryl is slow in neutral solutions. Little is known about the fate of carbaryl in surface water. Laboratory studies with pond water have shown that carbaryl is chemically hydrolyzed very rapidly in pond water to 1-naphthol. Enrichment of the pond water with bacterial isolates enhanced the degradation of carbaryl and 1-naphthol (Hughes, 1971). As would be expected, the persistence of carbaryl in natural water is highly influenced by the pH and temperature of the aquatic environment (Aly and El-Dib, 1971). A study of the persistence of carbaryl in estuarine water and mud in laboratory aquaria revealed approximately 50% disappearance of carbaryl in 38 days at 8C. Most of the decrease was accounted for by the production of 1-naphthol. At 20°C after 17 days, carbaryl had almost completely disappeared. Hydrolysis was accelerated by increasing temperature and by exposure to sunlight. It is evident from these studies that carbaryl is relatively nonpersistent in water.

Tolerances of carbaryl range from 5 ppm to 12 ppm on a wide variety of food crops and are generally 100 ppm on forage crops. The acceptable daily intake for carbaryl has been established by WHO/FAO at 0.01 mg/kg/day. Market Basket Surveys conducted by the Food and Drug Administration showed declining residues of carbaryl in composite samples from 1964-1970. The maximum level detected would result in a daily intake of 0.0021 mg/kg. Carbaryl was found in 7.4% of the samples in 1964, the year of its maximum detection.

II. METABOLISM

The metabolism and degradation of carbaryl have been studied extensively in microorganisms, plants, insects, and mammalian systems, including cell cultures, *in vitro* preparations, and whole animals. The compound is readily metabolized in most systems. The predominant metabolites are 1-naphthol and its conjugates. Other hydroxylated metabolites are generally found in relatively minor quantities, depending on the plant or animal system investigated and the circumstances under which the tests are conducted. All the metabolites are less toxic to both insects and mammals than carbaryl. In general, metabolism of carbaryl and the appearance of its metabolites in water systems would create no significant hazard in addition to that of carbaryl itself.

III. HEALTH ASPECTS

A. Observations in Man

Male volunteers ingested carbaryl in daily doses of 0.06 and 0.12 mg/kg for a period of 6 weeks (Wills *et al.*, 1968). Blood chemistry, urinalysis, stool examination, and electroencephalographic studies showed no substantive changes that were attributed to carbaryl. A slight decrease in ability of the proximal convoluted tubules to reabsorb amino acids was noted in the higher-dose group, but the lower-dose group showed increased absorption, compared with controls. These slight deviations were reversed and absorption became normal after feeding ceased.

A number of studies of occupational exposure to carbaryl have been reported. None of these indicate a great hazard in spray applicators that use carbaryl (Hayes, 1971). Exposure of inhabitants of huts that had been treated with carbaryl resulted in measurable concentrations of 1-naphthol in urine (Vandekar, 1965). The maximal concentrations measured within 24 h after exposure were equivalent to 70% of that found to be the oral no-adverse-effect dosage in dogs. Blood cholinesterase in some of these subjects was decreased by 15% after a week of exposure.

In general, fatal human poisoning from exposure to carbaryl is extremely rare.

B. Observations in Other Species

Acute Effects. The acute toxicity of carbaryl in laboratory animals is moderate. The acute oral LD_{50} of carbaryl suspended in 0.25% agar is 500 mg/kg in male and 610 mg/kg in female rats. The LD_{50} values were about the same when other media were used as a vehicle (Union Carbide Corp., 1957, 1958a, Cited in USEPA, 1975l).

Acute toxicity in other animals is about the same as in rats. The acute oral LD_{50} in guinea pigs is 280 mg/kg when administered in 0.25% agar, and in rabbits under the same conditions, 710 mg/kg (Union Carbide Corp., 1957, Cited in USEPA, 1975l).

The dermal toxicity of carbaryl is quite low. The dermal LD_{50} of the wettable powder formulation of carbaryl tested on rabbits was reported to be above 2,500 mg/kg (Union Carbide Corp., 1957, Cited in USEPA, 1975l).

Intravenous injection of carbaryl in female rats (weight, 90-120 g) as a 5% solution in propylene glycol gave an LD_{50} of 17.8 mg/kg and in male rats, 23.5 mg/kg. Intraperitoneal injection in male rats gave an LD_{50} of 57 - 180 mg/kg. The intraperitoneal LD_{50} of carbaryl in male albino rabbits was 220 mg/kg (Union Carbide Corp., 1958a, Cited in USEPA, 1975l).

Subchronic and Chronic Effects. Feeding studies with carbaryl in rats gave a no-adverse-effect dosage of 65 mg/kg/day (Union Carbide Corp., 1956, Cited in USEPA, 1975l); this dosage was fed over a 90-day period. In a later study, a dosage of 104 mg/kg/day gave no adverse effect in rats, whereas 167 mg/kg/day reduced growth, increased liver weight, and slightly decreased cholinesterase activity (Union Carbide Corp., 1958b, Cited in USEPA, 1975l).

Carbaryl was fed in the diet of rats for 7 days at 50 and 250 mg/kg per day. There was no adverse effect at the lower dosage; the higher dosage reduced growth and decreased plasma, red-cell and brain cholinesterase. After 1 day on a diet free of carbaryl, cholinesterase rose to normal, indicating a high degree of reactivation of the carbamylated enzyme (Union Carbide Corp., 1960, Cited in USEPA, 1975l).

In 2-year feeding studies with rats, the no-adverse-effect dosage was 8.2 mg/kg/day; 10 mg/kg/day reduced growth and caused transient cloudy swelling of kidney tubules and cloudy swelling of central hepatic cords (Union Carbide Corp., 1956b, Cited in USEPA, 1975l).

In dogs, no adverse effects were observed during a year of oral administration by capsule 5 days/week at 7.2 mg/kg/day (Union Carbide Corp., 1958c, Cited in USEPA, 1975l).

Mutagenicity. No studies with mammals as test organisms have been reported to show mutagenicity due to treatment with carbaryl. In this dominant-lethal test, no evidence of mutagenicity was found (Weil et al., 1973). A similar study with ICR-Ha Swiss mice gave similar results (Epstein et al., 1972).

The bacterial systems *Bacillus subtilis* (Degiovanni-Donnelly et al., 1968) and *Escherichia coli* (Ashwood-Smith et al., 1972) have been used to assess the mutagenic potential of carbaryl. Both yielded negative results. However, two studies with the fruit fly, *Drosophila melanogaster*, have indicated mutagenicity. A 1% suspension of carbaryl in sugar syrup produced a 0.25% mutation rate within 24 h (Brzheskii, 1972). Inclusion of 1, 5, and 10 ppm in diets gave black and white-eyed flies at all concentrations and more males than females at the medium dosage (Hogue, 1972). However, the relevance of these studies to mammalian mutagenesis is questionable.

Carcinogenicity. Carbaryl has been extensively tested for carcinogenicity. All results obtained to date indicate that carbaryl is not a carcinogen.

Tests in A/Jax and C3H mice--strains that are especially susceptible to lung tumors and mammary tumors, respectively--that received subcutaneously injections of 10 mg of carbaryl in 0.25% agar showed no increased incidence of tumors, lung infection, or mortality (Union Carbide Corp., 1958a, Cited in USEPA, 1975l). Several 2-year studies have been conducted with rats and dogs, and an 80-week feeding study with CD-1 mice. In these studies, careful searches were made for tumors, and none attributable to carbaryl were found (Union Carbide Corp., 1958b, 1958c, 1961, Cited in USEPA, 1975l).

Similar lifetime-exposure studies with carbaryl have been conducted in CF-N rats (Weil and Carpenter, 1965) and unspecified strains of rats and mice (Carpenter et al., 1961; Weil and Carpenter, 1962, Cited in USEPA, 1975l). All these studies culminated in the Bionetics study of 1969 (Innes et al., 1969), in which over 100 pesticides were administered to mice at maximally tolerated dosages. Carbaryl was fed at a daily dose of 4.64 mg/kg for 18 months and was declared to be one of the compounds that did not increase the incidence of tumors. In addition, the Mrak Commission report listed carbaryl as one of

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only three pesticides that were judged as "not positive for carcinogenicity by appropriate tests in more than one species of test animal."

Reproduction. The feeding of carbaryl to rats revealed no effects on reproduction or on growth rate and micropathology of pups. Dosages as high as 200 mg/kg/day were involved in these studies (Union Carbide Corp., 1965, Cited in USEPA, 1975l). However, intubation with 100 mg/kg/day did show some decrease in the number of successful matings and the number of pups born alive (Union Carbide Corp., 1972, Cited in USEPA, 1975l).

In the three-generation rat study the male rats that received dosages as high as 200 mg/kg/day by either oral intubation or incorporation into the diet mated with groups of virgin females. The females were killed midway through their gestation periods to observe the number of viable or dead fetuses and the number of early or late resorption sites (Weil and Carpenter 1965, Cited in USEPA, 1975l).

Teratogenicity. Teratogenic effects were not found in treated pregnant female rats in various schedules at 25, 100, and 500 mg/kg/day. The highest dosage was very close to the single-dose LD_{50} (Union Carbide Corp., 1965, 1966, Cited in USEPA, 1975l).

Pregnant guinea pigs were treated by gastric intubation or by incorporation of carbaryl inthe diet in 64 dosage schedules at 50, 100, 200, and 300 mg/kg/day. No teratogenic effects were found (Union Carbide Corp., 1971, Cited in USEPA, 1975l).

The observations of Dougherty *et al*. (1971) of possible reproductive effects of carbaryl in Rhesus monkeys were statistically analyzed (Weil *et al*., 1972) and shown to be nonsignificant and not dose-related. No teratogenic effects were found at 20 mg/kg/day.

IV. CONCLUSIONS AND RECOMMENDATIONS

Carbaryl is a moderately toxic carbamate insecticide that is widely used in commercial agriculture and in homes and gardens. It was the first of this group of insecticides to be introduced and is still the most heavily used. The mode of action of carbaryl is inhibition of the acetylcholinesterase, although there is evidence that the inhibition is reversible under some conditions, in contrast with that caused by the organophosphorus insecticides. Hence, chronic studies have been concerned with measuring factors in addition to decrease in cholinesterase activity, to determine a no-adverse-effect dosage.

Long-term studies have been conducted in rats and dogs and have led to the establishment of no-adverse-effect concentrations for these species. In addition, corroborating studies have been done in rats and man for shorter periods. Carbaryl has a known mode of action, adequate chronic-toxicity studies have been done, and there is no evidence of teratogenicity, mutagenicity, or carcinogenicity. An ADI was calculated at 0.082 mg/kg/day based on these data. The available data and calculations of ADI are summarized in Table VI-36.

There are no pressing research needs with respect to carbaryl. Continued monitoring of the presence and amounts of carbaryl in food and water will be necessary.

TABLE VI-36. Summary of Chronic

Toxicity Data for Carbaryl

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-Adverse Effect Level or Lowest Minimal-Effect Level	Effect Measured	Reference
Rat	90 days		66 mg/kg/day	Plasma cholinesterase depression; liver weight; growth	Union Carbide 1958, cited in EPA 1975 1
Rat	90 days	104, 167 mg/kg/day	104 mg/kg/day	No adverse effect	Union Carbide 1958b, cited in EPA 1975 1
			167 mg/kg/day	Plasma cholinesterase depression; liver weight; growth	
Rat	2 yrs		8.2 mg/kg/day[c]	No adverse effect	Union Carbide 1958b, cited in EPA 1975 1
			15 mg/kg/day	Growth; swelling of kidney tubules and central hepatic cords	
Dog	1 yr		7.2 mg/kg/day	No adverse effect	Union Carbide, 1958c, cited in EPA 1975 1
Man	6 wks	0.06, 0.13 mg/kg/day	0.13 mg/kg/day	Blood chemistry; kidney function	Wills *et al.*, 1968

Using an uncertainty factor of 100, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{8.2}{100} = 0.082 \text{ mg/kg/day (ADI)},\ 0.082 \times 70^{a} \times 0.1^{b} = 0.574 \text{ mg/liter.}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse-effect level.

C. FUNGICIDES

1. DITHIOCARBAMATES

FERBAM, MANEB, ZINEB, NABAM, THIRAM AND ZIRAM (AND ETU)

1. INTRODUCTION

Dithiocarbamate pesticides constitute a group of fungicides useful in seed dressing, as soil treatment, and to control numerous plant diseases. The total U.S. production of dithiocarbamate fungicides is around 40 million pounds a year, sufficient for them to rank as a major pesticide group (NAS, 1975). The compounds are salts and coordination complexes of N-methyl-, and ethylenebis-dithiocarbamic acids. The disulfide oxidation product (Thiram) of dimethyldithiocarbamic acid is a third important type. Dithiocarbamate fungicides are synthesized by reacting a suitable amine (dimethylamine or ethylenediamine) with carbon disulfide under alkaline conditions to yield the alkali salt of the alkyl dithiocarbamic acid. Reacting these water soluble salts with aqueous solutions of salts of zinc, iron, or manganese results in the precipitation of the corresponding highly insoluble metallo-salts which are the major commercial products (Melnikov, 1971). Alternatively the metallo-salts are produced by reaction of metal oxides with the appropriate amine and carbon disulfide. In addition, certain coordination products are produced such as the ammoniate of zinc EBDC (with EBDC acid and cyclic anhydrosulfide) designated as Polyram and the zincate of manganese EBDC designated as Dithane M-45 (Melnikov, 1971). The EBDC salts and coordination products are relatively low in toxicity; however, the occurrence of ethylenethiourea (ETU) as a major decomposition product of EBDC presents a potential hazard since it is goitrogenic in laboratory animals and may produce thyroid carcinoma.

The zinc (Ziram) and iron (Ferbam) salts of dimethyldithiocarbamic acid are the major N,N-dimethyldithiocarbamate fungicides. Both have low solubility in water: Ziram, 65 ppm at 25°C; Ferbam, 120 ppm at 20°C. The compounds are widely used because of their relatively great fungicidal activity, simplicity of production and low cost.

The zinc (Zineb), manganese (Maneb) and sodium (Nabam) salts of ethylene-bis-dithiocarbamic acid are the major ethlene-bis-dithiocarbamate (EBDC) fungicides. Amoben (the diammonium salt) and Nabam (the disodium salt) are sometimes used in preparation of Maneb and Zineb at the site of application, because they can be marketed as stable aqueous solutions. Mixing in the spray tank with zinc sulfate or manganese sulfate yields the precipitated Zineb and Maneb. Nabam is also used directly as a fungicide. Polyram (ammoniate of zinc EBDC) and Dithane M-45 (zincate of manganese EBDC) or Mancozeb (zinc complexes of Zineb and Maneb, respectively), and Dithane S-31 (nickel complex of Maneb) are other important market formulations. Except for the sodium and ammonium salts, all are extremely insoluble in water (Zineb, <1 ppm). These products are relatively low in toxicity; however, the occurrence of ethylene thiourea (ETU) as a major decomposition product of EBDC presents a potential hazard since it is goitrogenic in laboratory animals and may produce thyroid carcinoma.

Thiram, or tetramethylthiuramdisulfide, is an oxidation product of dimethyldithiocarbamic acid that has high fungicidal activity and is used particularly as a seed dressing. In addition to its agricultural use, it has important industrial uses, e.g., as a sensitizer in rubber synthesis. It is highly insoluble in water (Melnikov, 1971).

II. METABOLISM

N,N-Dimethyldithiocarbamates

The acute toxicity of N,N-dimethyldithiocarbamates is low. Oral LD_{50}'s in rats have been reported as: Ziram, 1400 mg/kg; and Ferbam, 34000 mg/kg (Hodge *et al.*, 1956).

When Ferbam labeled with radioactive carbon and sulfur was administered to Charles River male rats, uptake of 40-70% was observed during a 24-h period (Hodgson *et al.*, 1975). In rats receiving (^{35}S)Ferbam, 22.7, 18.1, and 1.0% of the radioactivity was found in urine, expired air, and bile, respectively. Little Sulfur-35 was found in tissues. With (^{14}C)Ferbam, 42.9 and 1.4% of the carbon-14 was found in the urine and the bile, respectively, and only 0.6% was recovered in expired air. The only expired metabolite was carbon disulfide. The metabolites in urine included inorganic sulfate, a dimethylamine salt, and a glucuronide of dimethyldithiocarbamate. With pregnant rats, (^{14}C)Ferbam radioactivity was shown to cross the placenta into the fetus in small but significant amounts. In lactating rats, (^{14}C)Ferbam treatment resulted in radioactivity in the milk, its absorption by the pups, and later excretion in the pups' urine. The authors reasoned that the significant metabolism occurs in the stomach, inasmuch as Ferbam is known to decompose to carbon disulfide and dimethylamine under acidic conditions. Ziram metabolism has apparently been studied only by Izmirova and Marinov (1975) in Bulgaria; although their work cannot be adequately interpreted, the appearance of a substantial part of the (^{35}S)Ziram metabolites as chloroform-soluble material indicates that a similar breakdown to carbon disulfide probably occurs.

Ethylene-bis-dithiocarbamates

The acute toxicity of EBDC is low, except for the soluble salts. Nabam and Amoben have an oral LD_{50} of 400 mg/kg in rats (Merck Index, 1968; Melnikov, 1971). In contrast, the LD_{50} of Zineb, Maneb, Polyram, and Dithane M-45 is about 5 g/kg or greater (Melnikov, 1971). The toxic effects observed at very high dosages are probably the result of the metal component.

In animal metabolism studies with (^{14}C)Maneb, Siedler *et al.* (1970) showed that nearly 55% of the administered dose was excreted as the metabolites ethylenediamine, ethylene-bis-thiuram monosulfide (ETM), and ethylenethiourea (ETU); metabolite excretion was mainly in the feces. Radiocarbon was cleared rapidly and did not accumulate in tissues.

III. HEALTH ASPECTS

A. Observations in Man. No data available.

B. Observations in Other Species

Acute Effects.

N,N-Dimethyldithiocarbamates

The rat oral LD_{50} values are 1400 mg/kg for Ziram and >4000 mg/kg for Ferbam (Hodge, *et al.*, 1956).

Ethylene-bis-dithiocarbamates

The acute toxicity of these fungicides are low except for the soluble salts. Nabam and Amoben have rat oral LD_{50} values of 400 mg/kg (Melnikov, 1971 and Merck Index, 1968). In contrast, LD_{50} values for the Zineb, Maneb, Polyram, and Dithane M-45 are on the order of 5 g/kg or greater (Melnikov, 1971). The toxic effects observed at very high dose rates are likely the result of the metal component.

Thiram

Thiram is considerably more toxic than most of the preceding dithiocarbamates, except Nabam and Amoben. Gaines (1969) reported oral LD_{50} values of 640 and 620 mg/kg in male and female rats, respectively. Other sources give the oral LD_{50} in rats as 780 mg/kg and in rabbits as 350 mg/kg (Melnikov, 1971; Merck Index, 1968).

Chronic Effects.

N,N-Dimethyldithiocarbamates

Long-term toxicity studies have indicated that Ziram and Ferbam are not tolerated as well as the acute-toxicity values would indicate.

Hodge et al. (1956) observed poor growth and development in rats fed Ferbam and Ziram at 0.25% of the diet. Both Ziram and Ferbam produced similar results, but Ziram was the more toxic when fed at 56 mg/kg to chickens (Rasul et al., 1974).

Melnikov (1971) stated that dogs administered Ziram at 5 mg/kg in the diet for 12 months showed no harmful effects. But reproductive abnormalities have been produced in rats and chickens given approximately 50 mg/kg (Chepinoga et al., 1970) and, 10 mg/kg produced no adverse effects (Ryazanova, 1967). In another case, Ziram pretreatment of female rats at 50 mg/kg for 50 days resulted in marked reduction in fertility and litter size, but had no effect on male fertility in mice (Cheeso et al., 1972).

Ethylene-bis-dithiocarbamates

The ethylene-bis-dithiocarbamates are generally well tolerated by laboratory animals during long-term administration, but it is difficult to define the threshold for toxic response, because the general presence of ethylenethiourea renders such decisions very difficult. ETU has been identified as a minor component of the commercial ethylene-bis-dithiocarbamate formulations (Johnson et al., 1962; Bontoyan et al., 1972) and is also formed metabolically (Seidler et al., 1970) or developed under conditions of environmental degradation (Ludwig et al., 1954; Vonk et al., 1976). ETU is goitrogenic, like thiourea and thiouracil, which are prototypes of antithyroid drugs. ETU concentrates principally in the thyroid, which then undergoes hyperplasia in response to inhibition of thyroxin production and the later continual stimulation by TSH from the pituitary. When groups of male rats were fed ETU at 0, 50, 100, 500, and 750 ppm for 1-4 months, effects were obtained at 100 ppm or greater. Body weight and food consumption decreased, the thyroid enlarged, and iodide uptake diminished in those animals. Histologic examinations of thyroid from the rats fed 500 and 750 ppm showed characteristic hyperplasia and adenomas, but sections of thyroid glands from rats fed 50 ppm were not different from the controls (Graham and Hansen, 1972). Weanling rats were fed Maneb or ETU over wide dosage ranges for 60 days, and similar effects were obtained (Sobotka, 1972). The highest dosage of Maneb used

(1,500 ppm) contained ETU as a contaminant at a concentration approximating the lowest dietary dosage of ETU used in the study (5 ppm), indicating that the ETU contaminant concentration was insufficient to account for the effects of Maneb on the thyroid. However, the metabolic conversion of ethylene-bis-dithiocarbamate to ETU, and perhaps to other antithyroid metabolites, contributes greatly to the thyroid changes.

Mutagenicity. No available data.

Carcinogenicity. One report attributed carcinogenic action to Ziram after implanting 15 mg subcutaneously; malignant tumors occurred in seven of 20 rats so treated (Andrianova et al., 1970). Because the dimethyldithiocarbamates are tertiary amines, they are candidates for possible nitrosation by reaction with nitrite at a low pH. Eisenbrand et al. (1974) demonstrated the formation of dimethylnitrosamine, a known carcinogen, after incubation of Ziram for 15 min in the rat stomach with an excess of nitrate. Ferbam was shown to behave similarly to Ziram during nitrosation. Ethylenethiourea does not arise from the dimethyldithiocarbamates, either as a metabolite or as a decomposition product, so it does not contribute to the toxicology of those fungicides. Hence, the goitrogenic and thyroid tumorigenic propensities of other dithiocarbamates are not associated with Ferbam or Ziram. Hodge et al. (1956), however, observed a small incidence of thyroid hyperplasia and tumors in rats given Ziram for 2 years, but not in those given Ferbam. The authors were cautious in ascribing the hyperplasia to an effect of Ziram. Dogs treated for a year also showed no thyroid pathology (Hodge et al., 1956). ETU was fed to 2 strains of mice at 215 mg/kg per day for 81 weeks (Innes et al., 1969). Hepatomas developed in both sexes and strains. The production of thyroid carcinoma and hepatoma by ETU constitutes the ultimate effect of long-term ingestion of ethylene-bis-dithiocarbamates and ETU (Tables 1 and 2). Humans occupationally exposed to Thiram have experienced contact dermatitis (Vonk et al., 1970) and ophthalmic disturbances (Sivitskaya, 1974).

Reproduction and Teratogenicity. Both Maneb and Zineb were found to be slightly teratogenic in rats given large single doses (1-4 g/kg and 2-8 g/kg respectively; the maximal no-effect was Maneb at 0.5 mg/kg and Zineb at 1 g/kg (Petrova-Vergieva et al., 1973)). Teratogenic effects have been demonstrated with ETU administered to rats and rabbits (Khera, 1973). Daily doses of 5 - 80 mg/kg produced dosage-related abnormalities in rats when fed either from before conception to day 15 of pregnancy or from conception to day 15 of pregnancy. Rabbits were less sensitive.

ETU was also found to have a small mutagenic index value (Seiler, 1976).

Thiram is fairly well tolerated in long-term studies, but has been associated with teratogenic effects in mice (Roll, 1971; Matthiaschk, 1973); rats have not been shown to be affected (Khera, 1969). Reproduction abnormalities in rats have been observed, however, that involved disturbed estros cycle and reduced fertility (Davydova, 1973). Cytogenetic and mutagenic effects have been reported by Russian investigators (Kurinnyi et al., 1972).

Immune System Effects. Considerable interest has been shown in effects of dithiocarbamates on various aspects of the immune defense systems. Ziram administered in the diet of female rats at 2.5 mg/kg for 9 months resulted in decreased antibody formation, decreased phagocytic activity, and decreased complement activity. Lymphatic blastogenic centers in the spleen were also reduced (Shtenberg et al., 1972).

Both Zineb and Maneb produce effects on the immune system similar to those of dimethyldithiocarbamates, but appear to be somewhat less active than Ziram. Zineb administered to rats and rabbits at 10 mg/kg daily produced no effects, but administration at 100 mg/kg led to reduction in antibody titers and phagocytic activity of leukocytes (Perelygin et al., 1971). Maneb given 5 times a week for 4.5 months at 150 mg/kg resulted in reduced resistance to infection. Chlorine compounds, such as DDT and PCB, are far more active in this respect than Zineb or Maneb (Olefir, 1974).

IV. CARCINOGENIC RISK ESTIMATES FOR ETU

ETU has produced hepatomas when given orally to mice (Innes et al., 1969). The available sets of dose-response data were individually considered as described in the risk section in the margin of safety chapter. Each set of dose-response data was used to statistically estimate both the life-time risk and an upper 95% confidence bound on the life-time risk at the low dose level. These estimates are of life-time human risks and have been corrected for species conversion on a dose per surface area basis. The risk estimates are expressed as a probability of cancer after a life-time consumption of 1 liter of water per day containing Q/ppb of the compound of interest. For example a risk of 1×10^{-6} Q implies a life-time probability of 2×10^{-5} of cancer if 2 liters per day were consumed and the concentration of the carcinogen was 10 ppb (i.e. Q=10). This means that at a concentration of 10 ppb during a lifetime of exposure to this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the U.S. is taken to be 220 million people this translates into 4400 excess lifetime deaths from cancer or 62.8 per year.

For ETU at a concentration of 1 µg/liter (Q=1) the estimated risk for man would be $1.6 \times 10^{-6}Q$. The upper 95% estimate of risk at the same concentration would be 2.2×10^{-6} Q.

V. CONCLUSIONS AND RECOMMENDATIONS

The dithiocarbamate fungicides are low in acute toxicity and do not present alarming properties during long-term administration to experimental animals, except at very high dosages. An acceptable daily intake has been temporarily set by the FAO/WHO (in 1974) at 0.005 mg/kg for both the dimethyldithiocarbamates (including Thiram) and the ethylene-bis-dithiocarbamates (FAO/WHO, 1975). That value represents a five-fold lowering from the previous value used by FAO/WHO for all dithiocarbamate fungicides. That decision was based, for the dimethyldithiocarbamates, on the recent evidence of teratogenic and mutagenic effects, as well as the possibility of nitrosation to form carcinogenic nitrosamines. For the EBDC compounds, the ETU problem and its associated teratogenic, mutagenic, and carcinogenic effects prompted the lowered values.

It could be held that ETU in water should be considered independently as a contaminant separate from the parent compounds. In light of the above and taking into account the carcinogenic risk projections it is suggested that very strict criteria be applied when limits for ETU in drinking water are established.

Based on long term feeding studies results, ADI's were calculated at 0.005 mg/kg/day for Maneb, Zineb and Dithane M-45; at 0.0125 mg/kg/day for Ziram and at 0.005 mg/kg/day for Thiram. The toxicity data on these compounds and calculations of ADI's are summarized in the following Tables: VI-37, 38, 39, and 40.

TABLE VI-37: Summary of No-Adverse-Effect Levels Estimated in Rats for Ethylene-bis-dithiocarbamate Fungicides and ETU, with Respect to Thyroid Hyperplasia and Sequelae

Compound	Highest levels with no-adverse effect, ppm	Lowest levels with minimum effect ppm	Reference
Zineb	5,000	10,000	Smith, 1953
Maneb	100	1,000	Haskell Lab, 1957
Maneb	100	1,000	Larson, 1964
Maneb	100	500	Balin, 1969
Dithane M-45	1,000	2,510	Rohm and Haas, 1972
Dithane M-45	100	1,000	Larson, 1964
Dithane M-45	300	1,000	Larson, 1965
ETU	63.1	159	Rohm and Haas, 1972
ETU	50	100	Graham and Hansen, 1972

TABLE VI-38: Summary of Chronic Toxic Levels*

Compound	Animal	Highest Levels with No-Adverse Effect, ppm	Lowest Level With Minimum-Effect ppm
Zineb	Mice	1,298	—
	Rats	—	500 (thyroid hyperplasia)
	Dog	2,000	10,000 (thyroid hyperplasia)
Dithane M-45	Rats	100	1,000 (thyroid hyperplasia)
	Dogs	1,000	—
Polyram	Rats	100	—
	Dogs	300	—
Maneb	Mice	158	—
	Rats	25	250 (thyroid hyperplasia)
	Dogs	80	800 (clinical effects)
ETU	Mice	—	646 (hepatoma)
	Rats	—	175 (thyroid carcinoma)
	Rats	—	5 and 25 (increased vascularity of thyroid)
	Rats	—	125 (thyroid hyperplasia)
	Mice	—	215 (hepatoma)
Nabam	Mice	73	—

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*Taken from EPA, 1973. The Toxicology and Environmental Hazards of the Ethylene Bisdithiocarbamate Fungicides and Ethylene Thiourea, pg. 261.

TABLE VI-39: Summary of Chronic Toxicity Data for Ethylenebisdithiocarbamates

Species	Duration of Study	Dosage Levels & No of Animals Per Group	Highest No-Adverse Effect Level or Lowest Minimal Effect Level	Effect Measured	Reference
ZINEB					
Rat	30 days	500-10,000 ppm, 10 animals per group	10,000 ppm	Thyroid hyperplasia	Smith et al., 1953
Mouse	18 mths	1,298 (464 mg/kg), 18 males, 18 females	1,298 ppm	No effect	Innes et al., 1969
MANEB					
Rat	6 mths	100 and 500 mg/kg, daily	500 mg/kg	Thyroid hyperplasia Liver degeneration	Balin, 1973
Rat	16 wks	0-10,000 ppm	1,000 ppm 100 ppm^{c,d} (5 mg/kg/day)	Thyroid hyperplasia; Increased liver/body wt. rates	Haskell Laboratory for Toxicology and Industrial Medicine Report No. 16-57
Rat	90 days	0-10,000 ppm	1,000	Thyroid hyperplasia	Larson, 1973
Mouse	18 mths	158 ppm 18 males, 18 females	158	No effect	Innes et al., 1969
DITHANE - M-45					
Rat	8 wks	0-2,510 ppm	2,510 ppm	Thyroid weight increase	Rohm & Haas, 1972
			10 ppm	Lowered thyroid iodide	"
Rat	90 days	0-150 ppm	150 ppm	Approx. threshold for thyroid pathology	Larson, 1964
Rat	90 days	0-10,000 ppm	1,000	Thyroid hyperplasia	"

Using an uncertainty factor of 1,000, suggested no-adverse effect level in drinking water for Maneb and Zineb is calculated as follows:

$$\frac{5}{1000} \doteq 0.005 \text{ mg/kg/day (ADI)},\ 0.005 \times 70^{a} \times 0.1^{b} = 0.035 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse effect level.

[d] Assume weight of rat = 0.4 kg and average daily food consumption of rat = 0.02 kg.

TABLE VI-40: Summary of Chronic Toxicity Data for Ziram and Thiram

Compound and Species	Duration of Study	Highest No-Adverse-Effect Level or Lowest-Minimal	Effect Measured	Reference
ZIRAM				
Rat	6 months pretreatment	50 mg/kg	Infertility embryotoxicity	Chepinoga et al., 1970
Rat		10 mg/kg	No-adverse effect	Ryazanova 1967
Rat	9 months	2.5 mg/kg	Immune suppression	Shtenberg et al., 1972
Rat	2 years	0.25% 0.25% diet (12.5 mg/kg)[c] 0.025%	Neurologic effect No-adverse effect No-adverse effect	Hodge et al., 1956
THIRAM				
Rat	3 generations	100 ppm (5 mg/kg/day)[c,d]	No-adverse effect	Khera, 1969
Mouse	days 6-17 of gestation	250 mg/kg	Teratologic threshold dosage	Roll, 1971

Using an uncertainty factor of 1000, suggested no-adverse-effect levels for Ziram and Thiram are calculated as follows:

Ziram: $\frac{12.5}{1000} = 0.0125$ mg/kg/day (ADI), $0.0125 \times 70^{a} \times 0.1^{b} = 0.088$ mg/liter

Thiram: $\frac{5}{1000} = 0.005$ mg/kg/day (ADI), $0.005 \times 70^{a} \times 0.1^{b} = 0.035$ mg/liter

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse-effect level.

[d] Assume weight of rat = 0.4 kg and average daily food consumption of rat = 0.02 kg.

i. PHTHALIMIDES

CAPTAN AND FOLPET

1. INTRODUCTION

Captan, or *N*-trichloromethylthio-4-cyclohexene-1, 2-dicarboximide, and Folpet, or *N*-trichloromethylthiophthalimide, were introduced in 1949 and 1952, respectively, as contact fungicides. Trade names include; for Captan, Merpan, Orthocide, Vancide 89, Vanguard K, Flit 406, and Amercide; and for Folpet, Phaltan and Folpan (Spencer, 1973). Domestic production of Captan was estimated at 17 million pounds in 1972 (NAS-NRC Pest Control, 1975); agricultural use of this agent was estimated at 6.5 million pounds in 1971 (vonRumker et al., 1975). Folpet production was estimated to be about 1.4 million pounds in 1974 (USEPA, 1975d).

Captan and Folpet are both broad-spectrum contact fungicides that are effective against a fairly wide range of fungi that cause plant diseases. They act by inhibiting fungal mycelial growth, but do not eradicate established fungal infection (USEPA, 1975b).

Captan is manufactured in a two-step synthesis from tetrahydrophthalimide and perchloromethylmercaptan. The technical product contains about 92% Captan, with sodium chloride, water, and unreacted tetrahydrophthalimide constituting the remainder (USEPA, 1975b). Folpet is synthesized commercially by the reaction of perchloromethylmercaptan with sodium phthalimide in a cold aqueous system. The technical product is 90-95% pure, and the major impurities are unreacted phthalimide (4.5%), water and calcium carbonate (up to 2.5% each), and sulfur (USEPA, 1975d).

Technical Captan is soluble in water at less than 0.5 ppm and soluble in chlorinated solvents to the extent of 1-2%. Folpet is insoluble in water at room temperature and only slightly soluble in organic solvents (Spencer, 1973).

Captan is rapidly degraded in natural soil by chemical as well as biologic means (estimated half-life, days to weeks). It has not been reported to be present in water, air, or nontarget plants (USEPA, 1975b). Folpet is stable when dry, but hydrolyzes slowly in water at room temperature. It has been reported to undergo photodegradation on plant surfaces to phthalic acid, chloride, and inorganic sulfur compounds. In the presence of sulfhydryl compounds, Folpet degrades rapidly to sulfur, phthalimide, and hydrochloric acid (USEPA, 1975d).

II. METABOLISM

Captan is rapidly absorbed from the gastrointestinal tract and rapidly destroyed in the blood. It does not accumulate in the tissues and reacts readily with thiol-containing compounds. The metabolites of Captan in mammalian systems have been indentified as tetrahydrophthalimide (which is further metabolized to 3-hydroxytetrahydrophthalamic acid, tetrahydrophthalimide epoxide, and 4,5-dihydroxytetrahydrophthalimide), chloride ions, thiophosgene, carbonyl sulfide, hydrogen sulfide, and a substituted thiazolidinethione (USEPA, 1975b). Folpet is rapidly absorbed in rats after oral administration. The breakdown products of Folpet are tetrahydrophthalimide and phthalimide (USEPA, 1975d).

III. HEALTH ASPECTS

A. Observations in Man

Captan was reported to be the thirty-ninth most frequently cited pesticide (11 cases in 1973) in the EPA Pesticide Accident Surveillance System (PASS), which lists accidents involving humans, animals, and plants (USEPA, 1975b). Folpet was involved in six cases of human poisoning between 1967 and 1975, according to the EPA Pesticide Episode Review System (USEPA, 1975d).

B. Observations in Other Species

Acute Effect. The acute oral LD_{50} of Captan in rats is about 10 g/kg of body weight, and it appears that this agent is also relatively nontoxic after acute oral ingestion in other species, although the data in other species are limited (USEPA, 1975b). Sheep appear to be more susceptible to the acute toxic effects of Captan than rats (Palmer, 1963). There does not appear to be any sex difference in the susceptibility of rats to Captan, but protein-depleted animals are more susceptible to Captan, as well as to other pesticides (Boyd and Krijnen, 1971).

Folpet is also relatively nontoxic to rodents (oral LD_{50}, 10 g/kg), but an intraperitoneal LD_{50} of 40 mg/kg in rats has been reported (USEPA, 1975d). The dermal toxicity of Folpet is also low (greater than 22,600 mg/kg in rabbits), and an inhalation exposure of 14 mg/liter for 1 h killed one of 10 rats.

Subchronic and Chronic Effects. Young male rats fed Captan in the diet at various dosages for 100 days exhibited an oral LD_{50} of 916 mg/kg/day, but some survivors had weight loss and inhibited spermatogenesis (Boyd and Carsky, 1971). Weight suppression was also noted in a 13-week study in which rats were fed Captan at a starting dietary dosage of 500 ppm. In this study, the dietary dosage was then increased weekly to reach 5,000 ppm at 4 weeks and 10,000 ppm at 7 weeks (Gray, 1954). The only toxic effect observed in a 2-year rat study with Captan (Weir, 1956) was weight reduction in the female rats fed the highest dietary dosage (5,000 ppm). There was some weight loss also during the last 1½ weeks of this 2-year study in the female rats fed Captan at 1,000 ppm. Testicular atrophy was observed in 3 of 24 male rats fed Captan in the diet at 10,000 ppm for 54 weeks, and growth decrease in both male and female rats (Weir, 1956). In another 2-year study, in which rats and mice were fed Captan in the diet at 1,000 and 2,000 ppm, no adverse effects on growth, mortality, or pathology were reported (Reyna et al., 1973).

Weight loss was observed in one-fourth of dogs fed Captan (50 mg/kg/day) for 66 weeks. In this study, four groups of dogs (two males and two females each) were given Captan at 10, 25, and 50 mg/kg/day by capsule (6 days/week). After 10 weeks of exposure, the highest two dosages were increased to 50 and 100 mg/kg/day. At 18 weeks, these dosages were further increased to 100 and 300 mg/kg/day (Fogelman, 1955). Enlarged kidneys and livers were observed in dogs fed Captan at 4,000 ppm for 66 weeks in a study that also included dietary dosages of 400 and 12,000 ppm (Fitzhugh, 1963).

Dystrophic changes were seen in the kidneys, lungs, spleen, stomach, and intestinal tract of rabbits given Captan orally at 500 mg/kg/day for 14 days (Szuperski and Grabarska, 1973). Toxic effects were not seen in monkeys fed Captan at 25 mg/kg/day for 11 days or in pregnant monkeys fed Captan in the diet at 75 mg/kg/day for 14 days (FAO/WHO CAPTAN, 1975). However, fetal mortality was seen at 12.5 mg/kg/day in an 84-day study in which monkeys were fed Captan at 6.35, 12.5, and 25 mg/kg/day (Courtney, 1970). There were no gross lesions or toxic manifestations observed in swine fed Captan-treated corn for 3 months at concentrations equivalent to 540 ppm or in weanling pigs fed diets containing Captan at 420, 840, and 1,680 ppm for 119 days (USEPA, 1975b).

Folpet was fed to rats (10 animals at each dosage) in a 12-week subacute study at 1,000, 2,300 and 10,000 ppm, with no reported effects on behavior, mortality, or gross or microscopic pathology, although there was a significant decrease in weight gain in the animals fed the highest dietary dosage (Weir, 1957). Similar results were obtained in another study in which groups of 30 rats of each sex were fed the same dosages of Folpet in the diet for 17 months (Ray and Calandra, 1961). Male and female dogs were given Folpet daily (5 days/week) at 1, 250, 1,000, and 1,500 mg/kg/day for 17 months. No adverse effects were noted during this study or in dogs sacrificed at the end of 12 and 17 months of exposure (Kay and Calandra, 1961).

Mutagenicity. Captan has been shown to be mutagenic in a number of microorganisms and in forward (but not in the reverse) mutation system with the *Neurospora crassa* test organism system (Malling and deSerres, 1970). Sex-linked recessive lethal mutations, translocations, and dominant lethal mutations were not seen in *Drosophila melanogaster*. Captan did not produce dominant lethal mutations when injected intraperitoneally into mice at 3.5 or 7 mg/kg (USEPA, 1975b). Both Captan and Folpet have been reported as positive mutagens in the *Salmonella* test by McCann *et al.* (1975).

Carcinogenicity. There was no increase in the number of tumors in mice exposed to Captan or Folpet in a carcinogenesis test in which 18 female and 18 male mice (C57BL/6 x AKR) were given the agents by gavage from day 7 to 28 (215 mg/kg) and fed Captan (560 ppm) or Folpet (603 ppm) for the rest of the 17 month exposure period (Innes *et al.*, 1969).

Reproduction. Reproductive studies in rats with Captan at dietary dosages of up to 1,000 ppm revealed no damage and no adverse reproductive effects, except for a slightly lowered lactation index in the third generation of the animals fed the diet containing 1,000 ppm (USEPA, 1975b).

Teratogenicity. Developmental anomalies were observed after single-dose administration of Captan (750 mg/kg) in pregnant hamsters on day 7 of gestation. No such effects were observed with a dosage of 500 mg/kg (USEPA, 1975b). In a three-generation rat study, the feeding of diets containing Captan at 1,000 ppm did not affect fertility, gestation, viability, or lactation index. Daily doses of Captan decreased sperm motility in rats (6 - 57 mg/kg/day) and in mice (20 - 25 mg/kg/day). The injection of Captan at 3 - 20 ppm into eggs resulted in an incidence of 7 - 8% malformations in the chick embryos, but later feeding studies in chickens did not reveal any terata (USEPA, 1975b).

IV. CONCLUSIONS AND RECOMMENDATIONS

Most of the chronic-oral-toxicity data on Captan and Folpet suggest that the no-adverse-effect or toxicologically safe dosage of these agents is about 1,000 ppm (50 mg/kg/day). However, on the basis of fetal mortality observed in monkeys exposed to Captan (12.5 mg/kg/day), the acceptable daily intake of Captan and Folpet has been established at 0.1 mg/kg of body weight by the FAO/WHO (cited in Vettorazzi, 1976).

Based on long term feeding studies results in rats and dogs, ADI's were calculated at 0.05 mg/kg/day for Captan and 0.16 mg/kg/day for Folpet. The toxicity data calculations of ADI's are summarized in Table VI-41 for Captan and in Table VI-42 for Folpet.

TABLE VI-41. Summary of Chronic Toxicity Data for Captan

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal Effect Level	Effect Measured	Reference
Rat	13 weeks	500-10000 ppm	10000 ppm (500 mg/kg/day)	weight reduction	Gray 1954
Rat	2 years	0-2000 ppm	2000 ppm (100 mg/kg/day)	no adverse effect	Reyna *et al.*, 1973
Rat	2 years	0-5000 ppm	1000 ppm (50 mg/kg/day)^{c,d}	no adverse effect	Weir, 1956
Rat	66 weeks	10000 ppm, 24 animals	10000 ppm (500 mg/kg/day)	testicular atrophy	Weir, 1956
Dog	66 weeks	0-300 mg/kg/day, 4 animals per group	300 mg/kg/day	weight loss	Fogelman, 1955
Dog	66 weeks	0-12000 ppm, 4 animals per group	4000 ppm (100 mg/kg/day)	enlarged liver	Fitzhugh, 1963
Monkey	14 days	0-75 mg/kg/day	75 mg/kg/day	no toxic effect	FAO/WHO, 1970
Monkey	14 days	0-25 mg/kg/day	12.5 mg/kg/day	fetal mortality	Courtney, 1970
Pig	119 days	0-1680 ppm	1680 ppm(108 mg/kg/day)	no adverse effect	FAO/WHO, 1978

Using an uncertainty factor of 1000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{50}{1000} = 0.05 \text{ mg/kg/day (ADI)}, \quad 0.05 \times 70^a \times 0.1^b = 0.35 \text{ mg/liter.}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse-effect level.

[d] Assume weight of rat = 0.4 kg and of dog = 10 kg, and of pig = 60 kg, average daily food consumption of rat = 0.02 kg, of dog = 0.25 kg and of pig = 2.4 kg.

TABLE VI-67: Summary of Chronic Toxicity Data for Folpet

Species	Duration of Study	Dosage Levels & No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest Minimal Effect Level	Effect Measured	Reference
Rat	12 weeks	0-10000 ppm, 20 animals per group	10000 ppm, (500 mg/kg/day)[d]	weight loss	Weir, 1957
Rat	17 months	0-10000 ppm	3200 ppm (160 mg/kg/day)[c,d]	no adverse effect	Weir, 1957
Dog	17 months	0-1500 mg/kg/day	1500 mg/kg/day	no adverse effect	Kay and Calandra, 1961
Mouse	17 months	215 mg/kg, 35 animals per group	215 mg/kg/day	no tumors	Innes *et al.*, 1969

Using an uncertainty factor of 1000, suggested no-adverse-effect in drinking water is calculated as follows:

$$\frac{160}{1000} = 0.16 \text{ mg/kg/day (ADI)}, \quad 0.16 \times 70^{a} \times 0.1^{b} = 1.1 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Test study from which to calculate suggested no-adverse-effect level.

[d] Assume weight of rat = 0.4 kg, and average daily food consumption of rat = 0.02 kg.

3. OTHER FUNGICIDES

HEXACHLOROBENZENE

I. INTRODUCTION

Hexachlorobenzene (HCB, Anticarie, Perchlorobenzene) was introduced as a cereal and seed treatment in 1945 and is registered in the United States as a fungicide for various cereal, vegetable, and other crops (Thomson, 1975). U.S. production for pest control is estimated at only 700,000 pounds (NAS, 1975), but HCB is encountered in much larger quantities as an intermediate or waste byproduct in various chemical syntheses, including that of pentachlorophenol, and as a contaminant of other pesticides, such as technical pentachloronitrobenzene (Borzelleca *et al.*, 1971) and DCPA (Kimbrough and Linder, 1974). HCB has also been identified as a prominent constituent of the air collected in the vicinity of a plant manufacturing perchloroethylene (Mann *et al.*, 1974).

HCB is produced commercially by exhaustive chlorination of benzene in the presence of a catalyst (Spencer, 1973). Analysis of three commercial HCB preparations showed that [illegible] contained pentachlorobenzene at 100-81,000 ppm (0.02-8.1%), octachlorodibenzo-p-dioxin at 0.05-212 ppm, and octachlorodibenzofuran (octa-CDF) at 0.35-58.3 ppm (Villanueva *et al.*, 1974). HCB has a very low solubility in water: only 6 ppb (Lu and Metcalf, 1975).

HCB is extremely lipophilic and resistant toward degradation. It has been identified in the tissues of marine birds (Gilbertson and Reynolds, 1972), predatory birds (Cromartie *et al.*, 1975; Vos *et al.*, 1968), and starlings (Nickerson and Barbehenn, 1975); surface water (Herzel, 1972); freshwater (Johnson *et al.*, 1974) and marine (Zitko, 1971) fish; and other aquatic organisms (Koeman *et al.*, 1969). HCB residues in edible freshwater fish reached 0.38 ppm, and in one case carp contained 62 ppm (Johnson *et al.*, 1974). Marine fish oils contained 0.06-0.38 ppm.

HCB residues have also been found in human adipose tissue and blood from different parts of the world (Abbott *et al.*, 1972; Acker and Schulte, 1970; Brady and Siyali, 1972; Burns and Miller, 1975; Curley *et al.*, 1973; Siyali, 1972), in human milk (Graca *et al.*, 1974; Stacey and Thomas, 1975), and in food products (Manske and Corneliussen, 1974; Manske and Johnson, 1975; Smyth, 1972). The EPA established interim HCB tolerances of 0.5 ppm in the fat of cattle and other domestic animals and 0.3 ppm in fat or milk and other dairy products.

HCB has been detected at 0.010 ppb in raw and 0.006 ppb in finished U.S. drinking water (USEPA, 1975j).

II. METABOLISM

In studies on the fate of [^{14}C]HCB in rats after intravenous administration, only 0.7 and 0.1% of the dose was recovered in feces and urine, respectively, over a 48-h period, and there was no conversion of the labeled HCB to [^{14}C]carbon monoxide or other volatile radioactive metabolites (Yang and Pittman, 1975). Fat contained the highest radioactivity.

Seven days after a single 5-mg/kg oral dose of [^{14}C]HCB in adult male rats, approximately 16% of the dose had been excreted in the feces and less than 1% in the urine (Mehendale *et al.*, 1975); 70% of the dose remained in the animal, with fat as the major depot. Metabolites in the urine included pentachlorobenzene, tetrachlorobenzene, pentachlorophenol, and four unknown compounds. The half-life of HCB in rats was found to be about 60 days (Morita and Oishi, 1975). Storage of dieldrin in the adipose tissue of rats is markedly decreased by HCB in the diet (Avrahami and Gernert, 1972).

In studies with rhesus monkeys, 17.1 and 1.8% of an intravenous dose of [^{14}C]HCB was excreted in feces and urine, respectively, over a period of 100 days (Yang and Pittman, 1975). As in rats, fat retained the highest amount of radioactivity.

In another study (Villeneuve, 1975), adult male Sprague-Dawley rats received HCB at 1, 10, and 100 mg/kg for 14 days and the tissues were then analysed for HCB. Two other groups, after 14 days of HCB feeding, were either fed an HCB-free diet *ad libitum* for 10 days or fed 25% of their normal food intake over the same period. HCB concentrations in tissues were fat > liver > lungs > kidneys > brain > spleen > heart > muscle > plasma. No appreciable losses of HCB occurred in the tissues over a 10-day period in the animals placed on a diet free of HCB. Animals fed restricted quantities of the HCB-free diet, however, showed a mobilisation of HCB stored within fat depots, which resulted in transfer of the compound into plasma and other tissues. Death occurred in the animals when brain HCB concentration exceeded 100 ppm.

Koss *et al.*, (1975, 1976) have recently studied the pharmacokinetics and metabolism of HCB in rats.

In vitro conversion of HCB to pentachlorophenol has been demonstrated in rat liver microsomal preparations (Lui and Sweeney, 1975), and a dechlorination system requiring reduced nicotinamide adenine dinucleotide phosphate in the liver and other tissues was found by Mehendale *et al.* (1975).

HCB crosses the placenta and accumulates in the fetus in a dose-dependent manner (Andrews and Courtney, 1976; Courtney *et al.*, 1976; Villeneuve *et al.*, 1974; Villeneuve and Hierlihy, 1975). In rats, the maternal liver had the highest HCB residue, followed by fetal liver, whole fetus, and fetal brain (Villeneuve and Hierlihy, 1975). This is in contrast with the results in rabbits, in which fetal liver contains HCB at concentrations 2-8 times higher than maternal liver.

III. HEALTH ASPECTS

A. Observations in Man

In the period 1955-1959, an outbreak of human poisoning occurred in Turkey as a result of the consumption of HCB-treated wheat (Cam and Nigogosyan, 1963; DeMatteis *et al.*, 1961; Schmid, 1960). Some deaths resulted, but the major syndrome was cutaneous porphyria, with skin lesions, porphyrinuria, and photosensitization. The estimated dosage was approximately 50-200 mg/day (0.71-2.9 mg/kg/day) for presumably long periods before toxic manifestations became apparent (Cam and Nigogosyan, 1963; Schmid, 1960).

B. Observations in Other Species

Acute Effects. The acute toxicity of HCB is relatively low, as evidenced by oral LD_{50} values of 3,500 mg/kg in rats, 2,600 mg/kg in rabbits, and 1,700 mg/kg in cats (Christensen *et al.*, 1974). In another report (Spencer, 1973), the acute oral LD_{50} in rats was given as 10,000 mg/kg.

Subchronic and Chronic Effects. HCB is considerably more toxic on prolonged exposure. Mortalities and severe weight loss occurred among Wistar rats and guinea pigs receiving daily 500 mg/kg oral doses of pure HCB over a period of 9-16 days (Villeneuve and Newsome, 1975). In a study by Hazelton Laboratories (USEPA, 1973c), rats were fed HCB at 5, 25, 125, and 625 ppm for 13 weeks. At 125 ppm, liver:body weight ratios were increased, and there were pathologic effects on the liver. No adverse effects were noted in animals fed 5 and 25 ppm.

In a study by Dow Chemical Company, gross and histopathologic alterations occurred in the livers of female weanling rats fed HCB at 30, 65, and 100 mg/kg/day for 30 days (USEPA, 1973c). No adverse changes were observed in rats fed 1, 3, or 10 mg/kg/day. In a second study by the same group, rats fed 20 mg/kg/day for 13 days developed neurotoxic symptoms and increased liver:body weight ratios; at 6 mg/kg/day, there was only slight skin twitching and nervousness, but a significant increase in liver:body weight ratio; no toxic effect was seen at 2 mg/kg/day.

Rats and rabbits fed HCB at 5,000 ppm in the diet died in 8-12 weeks, after showing severe neurologic symptoms (DeMatteis et al., 1961). There was a substantial increase in urinary porphyrin excretion after about 6 weeks; at death, there was substantial tissue porphyrin deposition in the animals. Guinea pigs and mice were much more susceptible to HCB; animals fed 5,000 ppm died after 8-10 days with marked neurologic signs. Before death, the latter animals developed moderate to severe porphyria.

Male and female Charles River rats received diets containing HCB at 0.5, 2.0, 8.0, and 32.0 mg/kg/day over a period of 12 weeks (Kuiper-Goodman et al., 1977a). Female rats were more sensitive than males to the toxic effects of HCB; 25% of the females and none of the males died at the highest dosage. Females also developed more severe porphyria, with high porphyrin concentrations in the liver. Males at the two highest dosages showed a significant increase in liver weight, and this was correlated with increased hepatic mixed-function oxidase activity and increases in the smooth endoplasmic reticulum. Additional information (Kuiper-Goodman et al., 1976b), presumably on the same study, indicated that tissue HCB residues had reached a plateau before 104 days. Tissue HCB concentrations were highest in adipose tissue, after which the order was liver > brain > serum. At the two highest dosages--8.0 and 32.0 mg/kg/day--liver:body weight ratios were increased in both sexes. Pathologic examination showed increased hepatocyte size due to proliferation of smooth endoplasmic reticulum. This was correlated with increased activities of drug metabolizing enzymes, which persisted long after animals were placed on an HCB-free diet. Females developed porphyria, which persisted after the rats were removed from the HCB diets.

Chronic ingestion of HCB at 2,000 ppm in the diet of adult male Sprague-Dawley rats resulted in hepatocellular degeneration and increases in the amounts of porphyrin and porphyrin precursors in the liver and excreta (Ockner and Schmid, 1961).

Male and female Sprague-Dawley rats were fed diets containing HCB at 10, 20, 40, 80, and 160 ppm for 9 or 10 months (Grant et al., 1974). Porphyria developed in rats fed 40 ppm and above, and the prophyria was much more severe in females than in males. Weight gains were reduced in female rats fed 80 and 160 ppm. Rats of both sexes showed increased liver:body weight ratios after receiving 80 or 160 ppm. Hepatic mixed-function oxidase activity was increased in male rats fed 40 ppm or more, but was unaltered in females. The pharmacologic activities of pentobarbital and zoxazolamine, however, were shortened in rats of both sexes fed 20 ppm or above. HCB residues in liver were similar in males and females and were dose-dependent.

Groups of weanling Sherman rats were fed technical HCB at 100, 500, and 1,000 ppm for a 4-month period (Kimbrough and Linder, 1974). No rats died in the control and 100-ppm groups, 2 of 10 males and 14 of 20 females died at 500 ppm, and 3 of 10 males and 19 of 20 females died at 1,000 ppm. Increased ratios of liver, spleen, adrenal, lung, and kidney weights to body weights were found in weanling Sherman rats fed 500 and 1,000 ppm. Hyperplasia of the adrenal cortex and lung degeneration were observed in all HCB-fed groups, particularly in females. Pathologic effects on liver and heart were found in rats receiving 500 ppm and above, with females showing the most severe effects. Hemoglobin and hematocrit values were significantly decreased in females fed 100 ppm or more and in males fed 1,000 ppm.

Mixed-Function Oxidase Activity and Porphyria. HCB has been shown to be associated with the production of porphyria in humans and experimental animals (Cam and Nigogosyan, 1963; DeMatteis *et al.*, 1961; Ocker and Schmid, 1961). In HCB-treated animals, there are substantial increases in liver weight, in smooth endoplasmic reticulum, in mixed-function oxidase activity, and in cytochrome P-450 content (Carlson and Tardiff, 1975; Grant *et al.*, 1974; Kuiper-Goodman *et al.*, 1975a,b; Turner and Green, 1974; Wade *et al.*, 1968). It is noteworthy that HCB apparently induces primarily the hepatic cytochrome P1-450 system, rather than the P-450 system (Turner and Green, 1974).

Porphyria resulting from ingestion of HCB is much more severe in female than in male animals (Grant *et al.*, 1974). HCB is known to induce increased activity of mitochondrial δ-aminolevulinic acid (ALA) synthetase (Myakoshi and Kikuchi, 1963). The HCB-induced porphyria, however, is not simply related to an increase in ALA synthetase activity, inasmuch as a twofold increase in the activity of that enzyme (the rate-limiting step in heme synthesis) cannot explain the observed massive increase in porphyrins in HCB-treated animals (Wade *et al.*, 1968). Moreover, although hemin normally exerts a feedback function to suppress ALA synthetase activity, HCB porphyria cannot be suppressed by hemin (Strik, 1973).

Recent evidence (Sweeney, 1976) suggests that a contaminant of technical HCB may be more active than HCB in producing porphyria in experimental animals. Porphyria develops in mice fed technical HCB at 1,000 ppm in about 6 weeks. To produce the same degree of porphyria in 6 weeks in mice with pure HCB, it was necessary to feed 2,500 ppm. Sweeney also presented preliminary evidence that HCB is actually converted by mixed-function oxidase systems in the liver to a reactive metabolite that then covalently binds to tissue macromolecules and that this produces the porphyria.

Mutagenicity. For dominant-lethal tests, 4 groups of 15 male Wistar rats each were given HCB orally at 20, 40, or 60 mg/kg for 10 consecutive days (Khera, 1974). After mating trials, there were no significant differences between test and control groups.

Carcinogenicity. HCB is currently being tested for carcinogenicity (IARC, 1974, 1975).

Reproduction. HCB at dietary concentrations of 10, 20, 40, 80, 160, 320, and 640 ppm was fed to Sprague-Dawley rats, and four generations of rats were raised (Grant *et al.*, 1975). The two highest dietary concentrations were toxic to the F generation, and 50 and 20%, respectively, of the females died. The viability index was zero in the F a and F b generations for rats fed 320 and 640 ppm and only 55% for the 160-ppm group. The lactation index decreased from 30% for the F a and F b generation pups to 0% for the F2a and F2b generation pups in the 160-ppm group, from 93% in the F generation to 40% in the F generation in the 80-ppm group.

Teratogenicity. No gross abnormalities were present in rat pups, but weight gain was affected by HCB treatment.

Teratogenic studies were carried out in Wistar rats given HCB in single daily doses of 10, 20, 40, 60, 80, or 120 mg/kg on days 6-9, 10-13, 6-16, or 6-21 of gestation (Khera, 1974). The 80- and 120-mg/kg doses caused maternal neurotoxicity and a reduction in fetal weight. In the fetuses, the incidence of unilateral and bilateral fourteenth rib was significantly increased over control values when doses of 20 mg/kg/day or more were administered on days 10-13, 6-16, or 6-21 of gestation. Sternal defects in the fetus were observed after 20 mg/kg/day on days 6-21 of gestation. Because these effects were not reproduced in later trials at up to 60 mg/kg given during the period of organogenesis, however, the teratogenic potential of HCB in the rat is doubtful. Oral administration of pure HCB at 100 mg/kg to CD-1 mice on days 7-16 of gestation, however, produced cleft palates and some kidney malformations (Courtney *et al.*, 1976).

IV. CONCLUSIONS AND RECOMMENDATIONS

The acute toxicity of HCB is relatively low, but subchronic or chronic exposure of laboratory animals or humans to HCB results in the development of severe porphyria, especially in females. An ADI was calculated at 0.001 mg/kg/day based on a 10-month feeding study in rats. The toxicity data and calculations of ADI are summarized in Table VI-43. A conditional acceptable daily intake of 0.0006 mg/kg/day was derived by the FAO/WHO as the upper limit for residues. The FAO/WHO suggested extreme caution with the compound and indicated that available information is insufficient to establish a firm acceptable intake for HCB.

HCB can be readily determined by electron capture gas chromatography at concentrations as low as 0.0001 ppb.

There are a number of puzzling differences in the highest no-effect and lowest-minimal-toxic-effect dosages found for HCB in rats (Table VI-43). These differences may be the results of using different rat strains or different HCB formulations in the various studies. They may also result from the use of HCB of uncertain purity. The source of the observed variations should be established. No subchronic- or chronic-toxicity studies have been conducted with HCB in mammalian species other than rats. It is especially important to conduct 2-year feeding experiments and carcinogenicity studies with HCB in two species, because HCB has been found to be extremely toxic on long-term exposure and is on the list of suspected carcinogens.

TABLE VI-41. Summary of Toxicity Data for HCB

Species	Duration of Study	Dosage Level and Number of Animals per Group	Highest No-adverse-Effect Level or Lowest Minimal-Effect Level	Effect Measured	Reference
Quail	90 days	0-80 ppm in diet, 15 animals per group	1 ppm (0.14 mg/kg/day)[d]	no toxic effect	Vos *et al.*, 1971
Rat	9-10 months	0-160 ppm in diet, 18 animals, per group	20 ppm (1 mg/kg/day)[c,d]	reduced sleeping time	Grant *et al.*, 1974
Rat	13 weeks	0-625 ppm in diet	25 ppm (1.25 mg/kg/day)[d]	no toxic effect	EPA, 1973c
Rat	13 weeks	0-200 mg/kg/day orally, 5 animals per group	8 mg/kg/day	no toxic effect	EPA, 1973c
Rat	12 weeks	0-32 mg/kg/day orally, 140 animals per group	2 mg/kg/day	no toxic effect	Kuiper-Goodman *et al.*, 1975a, 1975b
Rat	4 months	0-1,000 ppm in diet, 30 animals per group	100 ppm (5 mg/kg/day)[d]	adrenal hyperplasia and hematologic effects	Kimbrough and Linder, 1974
Rat	30 days	0-100 mg/kg/day	10 mg/kg/day	no toxic effect	EPA, 1973c

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Using an uncertainty factor of 1,000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{1}{1{,}000} = 0.001 \text{ mg/kg/day (ADI)},\ 0.001 \times 70^{a} \times 0.1^{b} = 0.007 \text{ mg/liter.}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Test study from which to calculate suggested no-adverse-effect level.

[d] Assume weight of rat = 0.4 kg and average daily food consumption of rat = 0.[illegible]2 kg.

PENTACHLORONITROBENZENE

I. Introduction

Pentachloronitrobenzene (PCNB, quintozene, terrachlor) was introduced in the United States in 1955 and is currently registered in this country as a soil fungicide treatment (USEPA, 1976a). The 1971 production by the single U.S. manufacturer was estimated at 3 million pounds (USEPA, 1976a; Lawless et al., 1972), 60-70% of which was consumed domestically (USEPA, 1976a). A 40-50% increase in production capacity has just been completed (USEPA, 1976a).

PCNB is produced commercially by exhaustive chlorination of nitrobenzene (USEPA, 1976a). Technical-grade PCNB contains an average of 97.8% PCNB, 1.8% hexachlorobenzene (HCB), 0.4% 2,3,4,5-tetrachloronitrobenzene (TCNB), and less than 0.1% pentachlorobenzene (Borzelleca et al., 1971). PCNB is only slightly soluble in water (0.44 mg/liter at 20°C).

FDA residue studies from 1964-1969 found PCNB residues in 0.7% of the leaf and stem vegetables sampled (USEPA, 1976a). Residues ranged from less than 0.005 - 0.42 ppm, with an average of 0.01 ppm. A tolerance of 0.1 ppm has been established for a number of vegetable and other crops, except peanuts, for which it is 1.0 ppm.

II. METABOLISM

After oral administration of PCNB to rabbits, 62% of the dose was found unchanged in the feces, 12% was excreted as pentachloroaniline (PCA), and 14% was excreted as N-acetyl-S-pentachlorophenylcystine (Betts et al., 1955).

After feeding of technical PCNB for 33 weeks to rats (at up to 500 ppm) and for 2 years to beagles (at up to 1,080 ppm), no PCNB was found in the tissues, but trace amounts of PCA and methylpentachlorophenylsulfide (MPCPS) were detected in various tissues and fat (Borzelleca et al., 1971). In rats fed PCNB at 500 ppm, the impurity HCB was detected in the greatest quantities, with 29.7, 1.93, and 6.43 ppm in muscle, liver, and kidneys, respectively. HCB was also the major residue found in dogs, with 6.41, 9.40, 7.28, 7.57, 0.65, and 1.37 ppm in kidneys, brain, muscle, liver, fat, and blood of animals fed PCNB at 1,080 ppm. The impurity pentachlorobenzene also was detected, at lower concentrations, in the tissues of the PCNB-fed animals.

No PCNB was found in the body fat of rats fed diets containing PCNB at 50 or 500 ppm for 7 months (Kuchar et al., 1969). Only trace amounts of pentachlorobenzene were found, but

HCB appeared at 117 ppm in the fat of rats fed PCNB at 500 ppm. Small amounts of PCA and MPCPS were also detected in the body fat.

PCNB was not detected in maternal tissues or 22-day-old fetuses after daily oral administration of doses of 50, 100, and 200 mg/kg to rats on days 6-15 of gestation (Villeneuve and Khera, 1975). Similar doses of pentachlorobenzene, however, accumulated to an appreciable extent in both maternal and fetal tissues.

In mice, four daily oral doses of PCNB (500 mg/kg) led to the appearance of PCA and MPCPS metabolites in fatty tissue of pregnant mice and fetuses; this indicated transplacental passage of these metabolites (Courtney, 1973; Courtney et al., 1976). PCNB was found mainly in the maternal tissues.

In dogs fed a diet containing PCNB at 5 or 1,080 ppm for 2 years, no PCNB was detected in muscle, kidneys, fat, or liver, and only trace amounts in the urine at 1,080 ppm (Kuchar et al., 1969). PCNB was present in the feces at both dosages. Pentachlorobenzene and HCB were detected in all samples. The PCNB metabolites PCA and MPCPS were detected in various fractions at both dietary PCNB dosages.

The present evidence from metabolic studies indicates that PCNB is rapidly metabolized to 2 major metabolites (PCA and MPCPS) and 2 minor ones (TCNB and pentachlorothiophenol). Two impurities of technical PCNB, HCB and pentachlorobenzene, also are commonly found in tissue, urine, and feces. The major excretary route of PCNB and its metabolites is via the bile, and tissue retention is concentrated in body fat and to a lesser extent in muscle.

III. HEALTH ASPECTS

A. Observations in Man. No available data.

B. Observations in Other Species

Acute Effects. PCNB is a relatively nontoxic pesticide. Oral LD_{50} values of 1,200 and 1,650 mg/kg were found in rats for unspecified PCNB dosages and formulations (Christensen et al., 1974). Technical PCNB dissolved in corn oil yielded oral LD_{50} values of 1,710 and 1,650 mg/kg in male and female rats, respectively (FAO/WHO, 1970) and 1,743 mg/kg in male rats (Borzelleca et al., 1971). The oral LD_{50} of PCNB in dogs is greater than 2,500 mg/kg (Finnegan et al., 1958).

Subchronic and Chronic Effects. Male and female weanling albino rats were fed diets containing PCNB for a period of 3 months (Finnegan *et al.*, 1958). The male rats showed significant loss of body weight at 2,500 ppm, and the females showed a slight weight loss at 5,000 ppm. There was a significant increase in the liver:body weight ratios at 63.5 ppm and above in the males, but only at 635 ppm and above in the females. The kidney:body weight ratios showed a significant increase in the male rats at 1,250 ppm, but no significant changes in the females.

In a chronic-toxicity study with rats, diets containing PCNB at 25, 100, 300, 1,000, or 2,500 ppm in a commercial powder (20% PCNB; 77% Pyrax ABB, a pyrophyllite carrier; and 3% Armour Sticker, an adherence aid) were fed over a 2-year period (Finnegan *et al.*, 1958). Deaths during the 2-year study, however, did not correlate with dietary concentrations of the fungicide. Female rats showed a slight growth suppression at 100 ppm PCNB and above, but no toxic effect at 25 ppm. The fungicide was a growth stimulant for males, especially at 300 ppm. No significant histopathologic or hematologic changes were observed at any dosage.

The same PCNB formulation was fed to mongrel dogs over a 1-year period, but no significant effects were observed at dietary concentrations up to 1,000 ppm (Finnegan *et al.*, 1958). In another study (Borzelleca *et al.*, 1971), purebred beagles of both sexes were fed for 2 years a diet containing technical PCNB at 5, 30, 180, and 1,080 ppm added in corn oil solution. No significant differences in body weight or food consumption were observed, although a few males, including controls, had lost weight by the end of the study. Hematocrit values were significantly decreased at 18 months for males fed 30 and 180 ppm, but there was no significant change in males fed 1,080 ppm. No changes were found in the females. Liver:body weight ratios were increased in dogs fed 1,080 ppm. Histologic examination after a year showed no treatment-related lesions; after 2 years, cholestatic hepatoses with secondary bile nephrosis were found in dogs fed 180 ppm and, to a greater extent, in those fed 1,080 ppm.

In a 2-year feeding study (cited by FAO/WHO, 1970), groups of male and female dogs were fed diets containing PCNB (purity not specified) at 500, 1,000, or 5,000 ppm. Liver changes - including fibrosis, narrowing of hepatic cells, thick leukocyte infiltration, and increased size of the periportal region - occurred in all groups; the degree of damage was dose-related.

Because technical PCNB contains 1.8% HCB, it is important to consider the toxicity of this major contaminant. Chronic ingestion of 0.2% HCB in the diet of adult male Sprague-Dawley rats resulted in hepatocellular degeneration and profound increases in the amounts of porphyrin and porphyrin precursors in the liver and excreta (Ockner and Schmid, 1961). Increased ratios of liver, spleen, adrenal, lung, and kidney weights to body weight were found in weanling Sherman rats fed technical HCB at 500 and 1,000 ppm for a 4-month period (Kimbrough and Linder, 1974). Hyperplasia of the adrenal cortex, as well as lung pathology, was observed. Female rats developed much more severe porphyria than did males fed HCB at 40 ppm for 274 days (Grant *et al.*, 1974). Rats of both sexes showed increased liver:body weight ratios after the feeding of HCB at 80 and 160 ppm. Liver mixed-function oxidase activity, however, was increased only in males fed 40 ppm and above. Liver pathology and increased liver:body weight ratios were found in male and female Charles River rats fed HCB at 8 and 32 mg/kg/day over a 15-week period (Kuiper-Goodman *et al.*, 1975). Only females developed porphyria.

Mutagenicity. PCNB produced a positive mutagenic response in host cell reactive deficient strain of *Escherichia coli* B/r ochre at 10-15 mg/kg (Clarke, 1971). PCNB had a negative mutagenic response, however, at a 2 mg/ml on *coli* Gal (a noninducible galactose-negative mutant of *E. coli* 343) (Mohn, 1971). *In vitro* mutagenic testing with mutant strains of *Salmonella typhimurium*, *Saccharomyces cerevisiae*, *coli*, and *Bacillus subtilus* in the presence of a liver microsomal preparation apparently showed no effect of PCNB (Simmon *et al.*, 1976). Dominant-lethal tests with three concentrations of PCNB in the diets of mice failed to show any evidence of mutagenicity (Jorgenson *et al.*, 1976). PCNB was negative in the sex-linked lethal test in *Drosophila* (Vogel and Chandler, 1974).

Carcinogenicity. PCNB is listed as a suspected carcinogen (IARC, 1973). Two mouse hybrid strains, (C57 Bl/6 x C3H/Anf) F1 and (C57 Bl/6 x AKR) F1, were given a maximal tolerated oral dose of PCNB (464 mg/kg in 0.5% gelatin) daily, from the age of 7 days to the age of 28 days (but the absolute dosage was not corrected for increasing body weight) (Innes *et al.*, 1969). The animals were then transferred to a diet containing PCNB at 1,206 ppm, which was fed for 17 months. A significantly increased incidence of hepatomas was observed in both strains; 2 of 18 male and 4 of 18 female (C57Bl/6 x C3H/Anf) F1 mice developed hepatomas, compared with 8 of 79 and none of 87, respectively, in the controls. Of the (C57Bl/6 x AKR) F1 mice, 10 of 17 males and 1 of 17 females developed hepatomas, compared with 5 of 90 and 1 of 82 in the controls. The incidence of other tumors was similar in the treated and control mice.

In another study, stock albino mice of each sex were painted twice a week with 0.2 ml of a 0.3% solution of PCNB in acetone for 12 weeks. This was followed by twice-weekly paintings with a 0.5% solution of croton oil in acetone for 20 weeks (Searle, 1966). A control group was treated with acetone alone and then croton oil. The total numbers of skin tumors at the end of the croton oil treatment were 12 in 9 surviving controls and 50 in 13 survivors of the PCNB group. One tumor in the PCNB group was a squamous-cell carcinoma, and one in the control group was an infiltrating squamous-cell carcinoma.

Rats that received PCNB at 25-2,500 ppm as a commercial powder (containing 20% PCNB) in the diet for 25 months showed no malignant growths or histopathologic changes related to dietary dosages of the fungicide (Finnegan et al., 1958). No tumors were reported in a 2-year study in which rats received diets containing PCNB at 25-2,500 ppm.

No tumors were observed in mongrel dogs fed PCNB at 25-1,000 ppm for a year (Finnegan et al., 1958) or in purebred beagles fed PCNB at 5-1,080 ppm for 2 years (Borzelleca et al., 1971).

The PCNB metabolite TCNB produced a larger number of papillomas than PCNB when applied to the skin and then followed by croton oil treatment (Searle, 1966). Searle (1966) suggested that tumor production results from formation of a hydroxylamine derivative formed as an intermediate in the metabolic reduction of the nitro groups. The TCNB has a stable nitro group, whereas 36-37% of the absorbed dose of PCNB yields a mercapturic acid by displacement of the nitro group; this perhaps accounting for the higher incidence of tumors with TCNB.

Reproduction. In a three-generation reproductive study in rats, no adverse effects on any factor appeared to result from dietary dosages of PCNB through 500 ppm (Borzelleca et al., 1971).

Teratogenicity. When technical PCNB was administered orally at 500 mg/kg to pregnant female C57Bl/6 mice on days 7-11 of gestation, renal agenesis and cleft palate were produced with a high frequency in the offspring (Courtney, 1973; Courtney et al., 1976). The major contaminant, HCB (11% of the technical PCNB preparation), produced cleft palates and some kidney abnormalities in mice and was probably the major active teratogenic constituent of commercial PCNB. Nevertheless, purified PCNB (HCB at <20 ppm) at 500 mg/kg also produced a significant, but much lower, incidence of cleft palate and an increased fetal mortality. Another impurity of technical PCNB, TCNB, and the PCNB metabolite PCA were not teratogenic in mice or rats.

When oral PCNB dosages of 100 - 1,563 ppm in corn oil were administered to Charles River albino rats on days 6-15 of gestation, no significant differences from controls were noted on examination of the fetuses on day 20 (Jordan and Borzelleca, 1973). Intubation of PCNB at 50, 100, and 200 mg/kg in rats on days 6-15 of gestation produced no significant effects in fetuses at day 20 (Khera and Villeneuve, 1975). No embryolethal or teratogenic effects were found in Charles River CD rats at dosages up to 125 mg/kg/day (Jordan et al., 1975).

IV. CARCINOGENIC RISK ESTIMATES

PCNB has produced hepatomas when given orally to mice (Innes et al., 1969). The available sets of dose-response data were individually considered as described in the risk section in the margin of safety chapter. Each set of dose-response data was used to statistically estimate both the life-time risk and an upper 95% confidence bound on the life-time risk at the low dose level. These estimates are of life-time human risks and have been corrected for species conversion on a dose per surface area basis. The risk estimates are expressed as a probability of cancer after a life-time consumption of 1 liter of water per day containing Q/ppb of the compound of interest. For example a risk of $1X10^{-6}$ Q implies a life-time probability of $2X10^{-5}$ of cancer if 2 liters per day were consumed and the concentration of the carcinogen was 10 ppb (i.e. Q=10). This means that at a concentration of 10 ppb during a lifetime of exposure this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the U.S. is taken to be 220 million people this translates into 4,400 excess lifetime deaths from cancer or 62.8 per year.

For PCNB at a concentration of 1 μg/liter (Q=1) the estimated risk for man would be $9.1X10^{-8}$ Q. The upper 95% estimate of risk at the same concentration would be $1.4X10^{-7}$ Q.

IV. CONCLUSIONS AND RECOMMENDATIONS

PCNB has relatively low acute toxicity. Although without effect in the rat and dog, PCNB appears to be carcinogenic in two strains of mice. In light of the above and taking into account the carcinogenic risk projections, it is suggested that very strict criteria be applied when limits for PCNB in drinking water are established. The chronic-toxicity data are summarized in Table VI-44.

A lower limit of detection of PCNB by gas chromatography was 0.01 ppm. A temporary acceptable daily intake of PCNB has been established for humans by the WHO at 0.001 mg/kg.

Most of the subchronic- and chronic-toxicity studies on PCNB have used technical-grade material, which normally contains about

1.8% HCB, but in some cases as much as 11% HCB. It is therefore not clear whether HCB and other impurities significantly contribute to the observed toxicity of PCNB. Moreover, some of the studies have involved PCNB formulations containing relatively low concentrations of the fungicide. The subchronic and chronic studies, particularly the latter, should be repeated in two species with pure PCNB. Such studies are particularly warranted, because of the suspected carcinogenicity of PCNB. Additional long-term oncogenic studies should also be conducted in susceptible strains of mice and other experimental animals. In addition, the FAO/WHO has recommended (Vettorazzi, 1975b) further short-term studies to elucidate the difference in teratogenic activity between rats and mice; studies to explain the effects on the liver and bone marrow of dogs; and further studies on the toxicity of PCNB metabolites.

TABLE VI-44. Summary of Chronic and Subchronic Toxicity Data for PCNB

Species	Duration of Study	Dosage Level and Number of Animals per Group	Highest No-Adverse-Effect Level or Lowest Minimal-Effect Level	Effect Measured	Reference
Dog	2 yrs.	0-1,080 ppm in diet, 8 animals per group	5 ppm (0.125 mg/kg/day)[a]	no effect	Borzelleca *et al.*, 1971
Rat	2 yrs.	0-2,500 ppm in diet, 80 animals per group	25 ppm (1.25 mg/kg/day)[a]	no toxic effect in females	Finnegan *et al.*, 1958
Rat	3 mos.	0-5,000 ppm in diet, 14 animals per group	63.5 ppm (3.2 mg/kg/day)[a]	increased liver/ body weight ratios in males	Finnegan *et al.*, 1958
Dog	2 yrs.	0-5,000 ppm in diet, 6 animals per group	500 ppm (12.5 mg/kg/day)[a]	liver pathology	FAO/WHO, 1970

[This compound is an animal carcinogen.]

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[a] Assume weight of rat = 0.4 kg and of dog = 10 kg; assume average daily food consumption of rat = 0.02 kg and of dog = 0.25 kg.

d. FUMIGANT

P-DICHLOROBENZENE

I. INTRODUCTION

p-Dichlorobenzene (PDB, Paracide) came into use as an insecticidal fumigant about 1915 (Spencer, 1973; Thomson, 1975). Because of its high vapor pressure, over 90% of PDB's use involves vapor production by sublimation (IARC, 1974): 50% of its use is as a space deodorant and sanitizer (in toilets and refuse containers), 40% in moth control, and 10% in other applications (Anon., 1973). Total U.S. use of PDB in 1972 was estimated at 68 million pounds (IARC, 1974); production was estimated at 60 million pounds (NAS, 1975) or as high as 100 million pounds (Von Rumker et al., 1975). Uses include 25-30 million pounds per year for moth control (balls, crystals, powders), 25-30 million pounds per year for lavatory-space deodorant, and the remainder for other purposes. PDB is also used as an intermediate in the synthesis of dyes and other chemicals (IARC, 1974).

PDB is produced commercially by chlorination of benzene or chlorobenzene at high temperature in the presence of catalysts (IARC, 1974). The impurities in technical-grade PDB are m and o isomers. PDB is soluble in water at 80 ppm at 25°C (Spencer, 1973). o-, m-, and p-Dichlorobenzenes have been detected in U.S. drinking water at 1.0, less than 3.0, and 1.0 ppb, respectively (USEPA, 1975).

II. METABOLISM

After oral administration in rabbits, PDB is metabolized to 2,4-dichlorophenol and 2,5-dichlorocatechol conjugated with glucuronic or sulfuric acid (Azouz et al., 1955). The same two metabolites of PDB have been identified in man (Hallowell, 1959; Pagnotto and Walkley, 1965), and the amount of 2,4-dichlorophenol in the urine can serve as an index of PDB exposure. The phenolic metabolites are excreted as glucuronide and sulfate conjugates (Hallowell, 1959).

o-Dichlorobenzene is metabolized in the rabbit to 3,4-dichlorophenol and smaller amounts of 2,3-dichlorophenol, 4,5-dichlorophenylmercapturic acid, 3,4-dichlorocatechol, and 3,4-dichlorocatechol (Azouz et al., 1955).

Both o-dichlorobenzene and PDB bind to cellular constituents, apparently via initial formation of reactive arene oxide intermediates formed by action of liver mixed-function oxidase systems (Reid and Krishna, 1973). Although hepatic mixed-function oxidase activities are increased by treatment of rats with the *m* isomer, *o*-dichlorobenzene and PDB had no effect (Ariyoshi *et al*., 1975).

III. HEALTH ASPECTS

A. Observations in Man

There is evidence that accidentally inhaled or ingested PDB is quite toxic to humans. One case of pulmonary granulomatosis (Weller and Crellin, 1953) and two cases of hemolytic anemia (Campbell and Davidson, 1970; Hallowell, 1959) have been reported after exposure to PDB. A case of allergic purpura after exposure to PDB has also been described (Nalbandian and Pearce, 1965).

Girard *et al*. (1969) reported five cases of blood disorders in subjects exposed to *o*-dichlorobenzene and/or PDB: two cases of chronic lymphoid leukemia, two cases of acute myeloblastic leukemia, and one case of myeloproliferative syndrome.

No evidence of toxicity or hematologic changes was found in workers after exposure to air containing *p*-dichlorobenzene at 1-44 ppm (average, 15 ppm) for many years (Hollingsworth *et al*., 1958).

The U.S. Occupational Safety and Health Administration health standards for air contaminants require that no employee's exposure to PDB exceed an 8-h time-weighted average of 75 ppm in the workplace during any 8-h work shift (IARC, 1974).

Prolonged inhalation of PDB by two young women reportedly caused development of cataracts (Berliner, 1939). Attempts to produce cataracts in rats, guinea pigs, and rabbits (Berliner, 1939; Pike, 1944; Zupko and Edwards, 1949) by treatment with PDB, however, were unsuccessful.

Human adipose tissue in Japan contained PDB at an average of 2.3 ppm (Morita and Ohi, 1975). Ambient-air samples collected in Tokyo contained PDB at 2-4 μg/m³, whereas closets and bedrooms where PDB moth preparations were used contained 105-1,700 μg/m³.

B. Observations in Other Species

Acute Effects. The LD_{50} of PDB in rats after intraperitoneal administration is 2,500 mg/kg (Hollingsworth *et al*., 1956). The acute oral LD_{50} of PDB is 500-5,000 mg/kg in rats and 2,950 mg/kg in mice (Spencer, 1973). An oral LD_{50} of PDB of 500 mg/kg in rats and a minimal lethal subcutaneous dose of 142 mg/kg in mice have also been reported (Christensen *et al*., 1974).

The oral LD_{50} of o-dichlorobenzene is 500 mg/kg in rats, whereas the minimal lethal dose after intravenous administration is 326 mg/kg in rats (Christensen et al., 1976).

Subchronic and Chronic Effects. Rabbits subjected to inhalation exposure to PDB at about 800 ppm for 8-h periods, 5 days/week for as long as 12 weeks, developed tremors, weakness, nystagmus, and reversible nonspecific eye changes (Pike, 1944). Pike (1944) indicated that this concentration of PDB is 5-10 times the concentration that humans would voluntarily tolerate. Rabbits fed PDB at 1,000 mg/kg for 5 days/week developed similar toxicity symptoms after several months (Pike, 1944).

Young adult female rats received oral doses of PDB suspension 5 days/week over a period of 27 weeks (Hollingsworth et al., 1956). At 376 mg/kg, the liver showed slight cirrhosis and focal necrosis. At 188 mg/kg, slight increases in the average weights of liver and kidneys occurred.

Rabbits were given PDB orally at 1,000 mg/kg for 5 days/week for 31 weeks or 500 mg/kg for 5 days/week for a year (Hollingsworth et al., 1956). Mortalities occurred among animals given the higher dosage; weight loss, tremors, weakness, and liver pathology developed in rabbits at both dosages. No hematologic changes were observed.

Young adult female rats received o-dichlorobenzene orally at 18.8, 188, and 376 mg/kg for 5 days/week for 28 weeks (Hollingsworth et al., 1958). At the highest dosage, liver and kidney weights increased, spleen weight decreased, and liver pathology developed. At 188 mg/kg, slight increases in liver and kidney weight occurred. No adverse effect was detected at the lowest dosage.

It is difficult to reconcile these results with those of Varshavskaya (1968), who treated male albino rats orally with o-dichlorobenzene in sunflower oil at 0.1, 0.01, and 0.001 mg/kg daily for a period of 7 months. Serum and tissue enzyme alterations, behavioral abnormalities, and a marked reduction in hemoglobin, red-cell, and leukocyte concentrations occurred in animals receiving 0.1 or 0.01 mg/kg/day. No toxic effect was seen in animals given 0.001 mg/kg/day.

CARCINOGENICITY. No adequate studies on which to evaluate carcinogenicity have been carried out, but an association in man between leukemia and exposure to PDB has been suggested (IARC, 1974, 1975). PDB and o-dichlorobenzene are listed as suspected carcinogens (IARC, 1974, 1975). PDB is reported (Parsons, 1942) to have induced a transplantable sarcoma after injection into an irradiated mouse.

Mutagenicity and Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

PDB is used in such a manner that large amounts of it could enter surface water and humans could obtain substantial exposure by inhalation. In spite of its tremendous use in the United States (68 million pounds) and its suspected involvement in human blood dyscrasias, there is very little adequate information on its toxicity. An ADI was calculated at 0.0134 mg/kg/day based on the available data. The available toxicity data and calculations of ADI are summarised in Table VI-45.

Gas-chromatographic methods have been developed for PDB with a sensitivity of 380 pg/cm peak height, and PDB concentrations as low as 1.0 ppb in water have been analysed.

Apparently, no chronic-toxicity studies have been performed with PDB. There is no information on the reproductive effects, teratogenicity, mutagenicity, or carcinogenicity of PDB. This lack of information is disturbing, in view of the suspected role of PDB in human leukemia and its apparent ability to undergo metabolic activation and covalent binding to tissue constituents. Particularly disturbing is the very high degree of toxicity in rats that received p-dichlorobenzene at 0.1 or 0.01 mg/kg/day. The no-adverse-effect dosage in that study (0.001 mg/kg/day) was 1/13,400 of that found in other similar rat studies. The reason for this marked difference should be established.

TABLE VI-45. Summary of Chronic and Subchronic Toxicity Data for PDB and ODB

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-Adverse-Effect Level or Lowest Minimal-Effect Level	Effect Measured	Reference
PDB					
Rat	67 wks.	0-376 mg/kg/day, orally 10 females per group	13.4 mg/kg/day[c]	no toxic effect	Hollingsworth et al., 1956
Rabbit	1 yr.	0-1,000 mg/kg/day, orally, 5 animals per group	357 mg/kg/day	weight loss, tremors, liver pathology	Hollingsworth et al., 1956
ODB					
Rat	7 mos.	0-0.1 mg/kg/day, orally 7 animals per group	0.01 mg/kg/day	hematologic, behavioral, enzyme changes	Varshavskaya, 1967
Rat	88 wks.	0-376 mg/kg/day, orally, 10 females per group	13.4 mg/kg/day[c]	no toxic effect	Hollingsworth et al., 1958

Using an uncertainty factor of 1,000, suggested no-adverse-effect level in drinking water for both PDB and ODB is calculated as follows:

$$\frac{13.4}{1{,}000} = 0.0134 \text{ mg/kg/day (ADI)},\ 0.0134 \times 70^{a} \times 0.1^{b} = 0.094 \text{ mg/liter.}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse-effect level.

C. OTHER ORGANIC CONSTITUENTS

ACETALDEHYDE

I. INTRODUCTION

Acetaldehyde is used extensively in the manufacture of acetic acid, acetic anhydride, synthetic resins, and various dyes. It is soluble in water and biodegradable in water (Merck Index, 1968; EPA, 1975d). It has been found in 5 of the 10 water supplies surveyed by EPA with the highest concentrations in Philadelphia and Seattle at 0.1 μg/liter (EPA, 1975a).

II. METABOLISM

Acetaldehyde is metabolized in the rat via aldehyde dehydrogenase to acetate, which ultimately breaks down to carbon dioxide (Forsyth et al., 1973). It has been shown to interfere with mitochondrial oxygen consumption in rat liver and thus to interfere with energy production (Cederbaum et al., 1974).

III. HEALTH ASPECTS

A. Observations in Man

In a study of the effects of acetaldehyde inhalation in dogs, Egle (1970) showed that exposure at 134 ppm for 30 m resulted in mild upper-respiratory-tract irritation. Higher concentrations decreased the respiratory rate by inhibition of the central nervous system. Exposure at 50 ppm produced eye irritation; 200 ppm resulted in conjunctivitis (Silverman et al., 1946). Although there have been no systematic studies bearing directly on the effect of acetaldehyde in man, the effects of ethyl alcohol are indicative of the effects of acetaldehyde, because it is the major metabolite of ethyl alcohol. Furthermore, there is extensive human experience with acetaldehyde, as it is the principle metabolic buildup product of disulfiram therapy.

B. Observations in Other Species

Acute effects. The oral LD_{50} is 1,900 mg/kg in rats (Smyth et al., 1951) and 1,232 mg/kg in mice (Amirhanova and Latypova, 1967). Parenteral LD_{50}'s are 560 mg/kg in mice and 640 mg/kg in rats (Skog, 1950).

In studies of the effects of acetaldehyde inhalation in rats, 100% saturated air was shown to be fatal within 2 m of exposure. The lowest lethal concentration proved to be 16,000 ppm in 4 h;

concentrations up to 4,000 ppm for 8 h produced no fatalities (Smyth *et al.*, 1951). The effects of chronic acetaldehyde inhalation have also been examined in hamsters (Kruysse *et al.*, 1975). Inhalation of acetaldehyde has been shown to affect both blood pressure and heart rate (McCloy *et al.*, 1974; Egle *et al.*, 1973; Egle, 1972). It has been suggested that these effects are mediated through the release of catecholamines.

Mutagenicity. No available data.

Carcinogenicity. Rats showed some focal spindle cell sarcomas when given acetaldehyde subcutaneously approximately 100 times, once or twice a week (Shubik and Hartwell, 1969).

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

Human exposure to acetaldehyde probably antedates recorded history, inasmuch as acetaldehyde is the major metabolite of ethyl alcohol. An additional source of widespread human exposure is tobacco smoke. The pharmacology and toxicology of acetaldehyde have been studied most extensively in its relationship to alcohol toxicity and human metabolism. Because of this background of human and laboratory experience, there appears to be no need to establish limits for acetaldehyde in drinking water.

BENZENE

I. INTRODUCTION

Benzene is produced by petroleum refining, coal tar distillation, coal processing, and coal coking. The United States production of benzene in 1973 was over 10 billion pounds (USITC 1975). It is used primarily as a chemical intermediate in the manufacture of styrene, cyclohexane, detergents, and pesticides.

It was reported that motor gasoline usually contains less than 5% benzene (Parkinson, 1971); the concentrations of benzene in the ambient air of gas stations were 0.001 - 0.008 mg/liter.

Benzene is slightly soluble in water (0.8 ppm by weight at 20°C). Four of the 10 water supplies surveyed by the EPA contained benzene (EPA, 1975 a,e) at levels between 0.1 - 0.3 μg/liter. The highest concentration of benzene reported in finished water was 10 μg/liter.

II. METABOLISM

Benzene is excreted rapidly. The metabolic products in the rat of benzene are phenol, hydroquinone, catechol hydroxyhydroquinone, and phenylmercapturic acid. Conjugated phenols have been reported by Williams (1975). In human retention studies, Nomiyama and Nomiyama (1974) reported 30% retention in man when exposed to 52 - 62 ppm for 4 h in air; Hunter and Blair (1972) noted that humans retained 230 mg after exposure to 80 - 100 μg/liter for 6 h. Benzene metabolism has been shown to be inhibited by 3-amino-1,2,4-triazole.

III. HEALTH ASPECTS

A. Observations in Man

Acute effects. Single exposures to benzene at 20,000 ppm have proved to be fatal in man. Industrial air concentrations of benzene have been reported to give rise to nausea, giddiness, headache, unconsciousness, convulsions, and paralysis (Browning, 1965; Eckardt, 1973).

Chronic effects. The chronic exposure of humans to benzene has been reported to produce thrombocytopenia, leukopenia, myelocytic anemia, and leukemia. Despite negative animal toxicity data, the evidence that benzene is a leukemogen for man is convincing. The pathogenesis of leukemia is usually preceded by many observed effects on the hematopoietic system (Snyder and Kocsis, 1975; Mallory *et al.*, 1939; Browning, 1965; Gerarde, 1960). The NIOSH (1974) recommended the occupational exposure to benzene at not in excess of 10 ppm determined as a time-weighted average exposure for up to a 10-h. workday. A recent review on the health effects of benzene (NAS, 1976) concludes that:

> Most cases of severe benzene intoxication have been reported in workers exposed to rather high concentrations of benzene under somewhat unhygienic working conditions. It is probable that all cases reported as "leukemia associated with benzene exposure" have resulted from exposure to rather high concentrations of benzene and other chemicals.
>
> It has been suggested in the literature that "benzene-induced leukemia" may occur only in individuals who are highly sensitive because of genetic constitution or because of synergistic action of other chemical or physical environmental agents. A co-leukemogenic role for benzene would explain the failure to induce leukemia in benzene-exposed animals.
>
> The state of the benzene literature makes it very difficult or impossible to reach a firm conclusion on the dose-response relationship in chronic exposure of humans to benzene. The details of the extent of exposures are either inadequate or absent. Even in cases where some concentrations of benzene are reported, the stated concentrations were based on occasional measurements of short durations. The role of benzene metabolism in its toxicity and the significance of benzene-induced chromosome aberrations are currently unclear. It appears that a metabolite of benzene may be responsible for its myelotoxic effects.
>
> Based on available literature, it can be concluded that benzene may be associated with leukemia; therefore, benzene must be considered as a suspect leukemogen. More definitive data are required for an accurate assessment of the myelotoxic, leukemogenic, and chromosome-damaging effects of benzene.

B. Observations in Other Species

Acute effects. In an acute study, it was shown that rabbits absorbed benzene through the skin and underwent anesthesia at 35,000 - 45,000 ppm. Benzene inhaled by mice at 60 mg/liter in air (18,750 ppm) caused lesions on lipoprotein membranes.

Chronic effects. In a series of chronic studies, bilateral cataracts were found in 50% of the rats exposed to benzene at 50 ppm for 600 h; at 60 - 883 ppm, rats became leukopenic. It has also been found that an inadequate dietary protein intake has some bearing on the development of benzene toxicity.

Mutagenicity. Some preliminary work suggests that benzene may induce mutagenic chromosomal alterations. Forni *et al.* (1971) have reported an increased incidence of various kinds of chromosomal breaks or aberrations in workers occupationally exposed to benzene. These observations are complicated by the fact that there were simultaneous exposures to other compounds.

Carcinogenicity. Although animal experiments have thus far proved negative, with respect to the carcinogenic properties of the compound (Ward *et al.*, 1975), there are some indications that benzene acts as a cocarcinogen in humans (Dobrokhotov, 1972, Smolik *et al.*, 1973).

Teratogenicity. There is no reported evidence of benzene-induced teratogenicity.

IV. CARCINOGENIC RISK ESTIMATES

On review of the original data from the carcinogenicity study by Ward *et al* (1975), it is concluded that the observed increased occurrence of granulocytic leukemia in benzene-treated animals is not statistically significant, even when time to response is incorporated into the analysis. Therefore, statistical extrapolation from these data would be unwarranted. An additional difficulty in extrapolation is posed by the fact that the experimental route of exposure was subcutaneous injection, whereas man's exposure would be through ingestion of drinking water.

Occupational studies on human exposure (Aksoy *et al*, 1972; Ishimaru *et al*, 1971; Aksoy *et al*, 1974a,b; Thorpe, 1974) do not contain adequate information on degree of exposure or size of population at risk. In addition, because the workers in benzene-related occupations were probably exposed to other chemicals, extrapolation of benzene-induced cancer risk from such data as these would be tenuous.

V. CONCLUSIONS AND RECOMMENDATIONS

The acute effects of benzene cover a wide range of signs and symptoms. The effects are transitory but may lead to more lasting chronic effects such as anemia; if exposure is continuous and great enough, leukemia is a strong possibility for susceptible members of the population. There are no dose-response data on animals and the data on humans are inadequate to calculate a risk estimate for benzene with mathematical models.

In summary, there is no adequate source of data (animal or human) on which to base a statistical extrapolation from high to low exposure. More data are needed on the mutagenicity and teratogenicity of benzene. The cocarcinogenic effect of benzene should be further explored. If data are available on industrial benzene exposure, then systematic monitoring should be started with a view to following the population groups at risk.

Before limits for benzene in drinking water can be established more extensive toxicological data must be gathered and evaluated.

BENZO(a)PYRENE

I. INTRODUCTION

Benzo(a)pyrene is a ubiquitous polycyclic aromatic hydrocarbon that is produced largely, if not exclusively, in the pyrolysis of naturally occurring hydrocarbons. It was isolated early in pure form from coal tar, one of the so-called industrial carcinogens. Benzo(a)pyrene is found as a constituent in coal, petroleum, shale, and kerosene. It has been reported that it is present in the combustion products of fuels and cigarette smoke.

Benzo(a)pyrene is very persistent in water and is soluble at 0.004 mg/liter at 27°C (Davis, 1942). It has been detected in finished water (EPA, 1976).

II. METABOLISM

The primary routes of benzo(a)pyrene excretion in mice and rats are the hepatobiliary and gastrointestinal tracts. The dihydroxy-, 3-hydroxy-, and 6-hydroxy- derivatives have been found in the liver, bile, and bowel (Berenblum and Schoental, 1943; Falk *et al.*, 1962; Sims, 1967, 1970a,b).

III. HEALTH ASPECTS

A. Observations in Man

There is no firm evidence that benzo(a)pyrene alone produces toxicity, including teratogenicity, mutagenicity, or carcinogenicity in humans. On the other hand, mixtures of compounds which contain benzo(a)pyrene as a constituent have been associated with cancer in man. In such cases the exact role of benzo(a)pyrene is difficult to assess

B. Observations in Other Species

Mutagenicity. Although there is no substantive literature on the mutagenic effects of benzo(a)pyrene, there have been indications that its metabolites bind to DNA. Benzo(a)pyrene is a positive mutagen in the *Salmonella*/microsome test (McCann *et al.*, 1975).

Carcinogenicity. The effects of benzo(*a*)pyrene have been examined for the most part in relation to carcinogenesis. In mice, a single oral 0.012-mg dose induced forestomach tumors (Pierce, 1961); in rats a single 100-mg dose (gavage,) produced mammary tumors (Huggins and Yang, 1962). Single subcutaneous and intramuscular doses that induced tumor formation were 0.062 mg, 0.004 mg, and 0.0025 mg in C3H, C57, and CFW Swiss mice, respectively. In rats and hamsters, the parenteral carcinogenic doses were 0.05 mg and 0.01 mg, respectively.

In chronic oral studies, carcinogenic effects were observed in mice after the administration of benzo(*a*)pyrene at 40-45 ppm for 110 days (Rigdon and Neal, 1966, 1969). Dontenwill and Mohr (1962) reported stomach tumors in hamsters after biweekly oral administration of the compound for 1 month. In mice, chronic dermal administration of a 0.001% solution three times a week induced benign and malignant skin tumors (Wynder *et al.*, 1957). Rats and hamsters were also shown to be sensitive to the induction of skin tumors with benzo(*a*)pyrene (Nakano, 1937; Shubik *et al.*, 1960).

In a study of the transplacental carcinogenic effects of benzo(*a*)pyrene, 2-4 mg on days 11, 13, and 15 of pregnancy induced tumors in the offspring of treated mice (Bulay and Wattenberg, 1970; Bulay, 1970). No other abnormalities were observed.

Teratogenicity. Rigdon and Rennels (1964) found one malformed fetus out of 7 litters of rats whose mothers had been exposed to benzo[a]pyrene at a level of 1 mg/g of diet during pregnancy. There were also many excess reabsorptions and dead fetuses.

IV. CARCINOGENIC RISK ESTIMATES

Numerous carcinogenesis studies have been conducted in rodents with oral administration of benzo(*a*)pyrene (IARC, 1973). Stomach tumors in mice have been observed in several studies, as well as leukemia and lung adenomas. In rats, mammary tumors and papillomas in the esophagus and forestomach have been found. In hamsters, tumors were found in the forestomach, esophagus, and intestine. No satisfactory human data are available.

In the above studies, the oral administration of benzo(*a*)pyrene showed evidence of dose-response relationships. However, it was generally fed for less than 6 months; this is not adequate for estimating lifetime effects. Thus, without specific biologic assumptions that relate short-term to lifetime effects, no reasonable risk estimates can be attempted.

V. CONCLUSIONS AND RECOMMENDATIONS

The occurrence of upper gastrointestinal tract tumors in animals fed benzo(a)pyrene, skin tumors at sites painted with it, and subcutaneous sarcomas at sites where it was injected demonstrates that benzo(a)pyrene is a potent contact carcinogen. In light of the above it is suggested that strict criteria be applied when limits for benzo(a)pyrene in drinking water are established. The available chronic toxicity data are summarized in Table VI-46.

TABLE VI-46. Summary of Chronic Toxicity Data for Benzo(a)Pyrene

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse-effect Level or Lowest Minimal-effect Level	Effect Measured	Reference
Mouse	110 days		40-45 ppm (oral)	Stomach tumors	Rigdon & Neal 1966, 1967, 1969
Hamster	1-5 mo.	biweekly administration	2-5 mg (oral)	Stomach tumors	Dontenwill & Mohr, 1962
Mouse			0.001% solution (oral)	Malignant skin tumors	Wynder et al. 1957
Rat	150 days	weekly paintings, 15 animals	0.5-1% solution	Skin tumors	Nakano, 1937
Hamster	40 wks.	biweekly paintings, 10 animals	0.01% solution	Skin tumors	Shubik et al. 1960

(This compound is a suspected human carcinogen as well as a confirmed animal carcinogen.)

BROMOBENZENE

I. INTRODUCTION

Bromobenzene (Monobromobenzene) is used as an intermediate in organic synthesis, and as additive in motor oil and fuels. During chlorination water treatment, bromobenzene can be formed in small quantities USEPA, (1975d). It is insoluble in water (CRC Handbook of Chemistry & Physics, 1970-1971). Bromobenzene was found in finished water in the lower Mississippi River area (EPA, 1972).

II. METABOLISM

Bromobenzene appears to be metabolized in the rat to an intermediate that can produce tissue damage (Reid, 1973). This damage is blocked by prior administration of piperonyl butoxide; thus, the damage may be due to a toxic metabolite. The metabolite is apparently produced in the liver and transported to the kidneys by the circulation. Phenobarbital pretreatment increases the liver toxicity of bromobenzene, but has little or no effect on the kidneys (Reid *et al*., 1971; Sipes *et al*., 1974). Bromobenzene may be metabolized to an epoxide (which causes the liver damage), excreted in the bile, reabsorbed through the enterohepatic circulation, and metabolized in several steps to p-bromophenyl mercapturic acid, which is then excreted in the urine (Reid *et al* 1971).

III. HEALTH ASPECTS

A. Observations in Man

Bromobenzene irritates the skin and is a central nervous system depressant in humans. Nothing is known about its chronic effects.

B. Observations in Other Species

Acute effects. In an inhalation study in rats, bromobenzene was administered daily for a 4-h period at 3 $\mu g/m^3$, without toxic effects; 20 $\mu g/m^3$ was a definite-effect dosage in similar tests (Shamilov, 1970). 1970).

Chronic effects. No available data.

Mutagenicity. Bromobenzene was not mutagenic in the *Salmonella*/microsome test (McCann *et al*, 1975).

Carcinogenicity. There is no evidence that bromobenzene is carcinogenic in animals and man.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the carcinogenicity, teratogenicity and long term oral toxicity of bromobenzene, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established. Since bromobenzene was negative on the *Salmonella*/microsome mutagenicity test, there should be less concern than with those substances which are positive.

BROMOFORM

I. INTRODUCTION

Bromoform (tribromomethane) is used in pharmaceutical manufacturing, as an ingredient in fire-resistant chemicals and gauge fluid, and as a solvent for waxes, greases, and oils (EPA, 1975d).

Bromoform is non-biodegradable in water. It is soluble at 1 part per 800 parts of water (Merck Index, 1968). Bromoform results from chlorination of precursors in raw water. Of 80 water supplies surveyed, 26 were positive results for bromoform in finished water, with a concentration range of <0.8 - 92 µg/liter (EPA, 1975a). Of the 83 Region V water supplies surveyed, 14% contained bromoform, at a mean concentration of less than 1 µg/liter; none of the raw water contained bromoform (EPA, 1975b).

II. METABOLISM

Lucas (1929) demonstrated in rabbits that bromoform administered rectally or by inhalation was biotransformed in the liver and that inorganic bromides were later found in tissues and urine. After rectal anesthesia with bromoform 0.3 - 1.2% of the dose was recovered in the urine as sodium bromide.

III. HEALTH ASPECTS

A. Observations in Man

No data are available on the adverse health effects of bromoform in man. An air exposure limit based on animal studies is listed in the Federal Register (1972) as 0.5 ppm, or 5 mg/m³.

B. Observations in Other Species

Acute effects. The subcutaneous LD_{50} in mice is 1,820 mg/kg (Kutob and Plaa, 1962). In an attempt to assess the liver toxicity of bromoform, Kutob and Plaa (1962) found that a subcutaneous dose of 278 mg/kg was negative in mice, whereas 1,113 mg/kg produced decreased liver function as well as hepatic histopathology. In rats, the maximal single oral dose survived was 6,578 mg/kg at 1 h, 2,099 mg/kg at 8 h, and 658 mg/kg at 24 h.

Dykan (1962) reported that injecting 100 - 200 mg/kg/day into guinea pigs for 10 days resulted in pathologic changes in kidney and liver.

Chronic effects. Inhalation by rats of 0.25 mg/liter of air for 4 h/day for 2 months produced disorders in prothrombin synthesis and glycogenesis in the liver and reduced renal filtration capacity; the threshold concentration was 0.05 mg/liter (Dykan, 1962).

Mutagenicity. Weakly positive in *Salmonella* test (Simmon and Poole, 1976).

Carcinogenicity. No available data.

Teratogenicity. No available data.

VI. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity and long term toxicity of bromoform, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

tert-BUTYL ALCOHOL

I. INTRODUCTION

tert-Butyl alcohol (t-butanol) is used as an alcohol denaturant, a solvent, a dehydration agent, and a chemical intermediate (The Condensed Chemical Dictionary, 1971). It is miscible in water (CRC Handbook of Chem. & Phys., 1970-1971). In the 10-city survey, only the finished water of Cincinnati contained tert-butyl alcohol (EPA, 1975a).

II. METABOLISM

Gaillard and Derache (1964) found, after administering tert-butyl alcohol orally to rats at 2 g/kg, that there was rapid absorption into the blood; 0.98% was excreted in the urine. After intraperitoneal administration in rats at 0.84 g/kg (Rietbrock and Abshagen, 1971), exponential elimination from the blood occurred, but more slowly than that of other aliphatic alcohols; the blood half-life was 13 h. Transformation by glucuronidation (24%) is the only metabolic pathway known. The possible conjugation is between the hydroxyl group, and glucuronic acid. There is potential for one of the methyl groups to be oxidized to β-hydroxyisobutyric acid (Williams, 1959). Oral administration of tert-butyl alcohol in rats elicited a threefold increase in liver microsomal enzyme activity 24 h later (Bechtel and Cornish, 1972).

III. HEALTH ASPECTS

A. Observations In Man

A slight erythema has been reported in man after exposure of skin to tert-butyl alcohol (Oettel, 1936), and it has been suggested that the compound is a skin irritant (Swartz and Tulipan, 1939). The United States occupational standard in air is listed in the Federal Register (United States Dept. of Labor, 1972.) at 100 ppm. A threshold limit value (TLV) has been set at 100 ppm, or 300 mg/m^3 (ACGIH, 1971).

B Observations In Other Species

Acute effects. The acute effects of tert-butyl alcohol have been examined in both mice and rats. The oral LD_{50} in rats is 3,500 mg/kg (Schaffarzick and Brown, 1957). In mice the subcutaneous LD_{50} is 5 ml/kg (Harada, 1937).

Chronic effects. No available data.

Mutagenicity. No available data.

Carcinogenicity. Hoshino et al. (1970) conducted a study to determine the carcinogenic activity of t-butylalcohol. Mice treated with an initiating dose of 4-nitroquinoline-1-oxide were examined after 270 applications of t-butanol, and no increase in carcinogenic activity was found.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenility, teratogenicity, and long term oral toxicity of t-butyl alcohol, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be estabished.

e-CAPROLACTAM

I. INTRODUCTION

e-Caprolactam (hexahydro-2H-azepin-2-one) is used in the manufacture of nylon, plastics, bristles, film, coatings, synthetic leather, plasticisers, and paint vehicles; as a cross-linking agent for curing polyurethanes; and in the synthesis of lysine (EPA, 1975d). The United States production of e-caprolactam in 1973 was over 656 million pounds (USITC, 1975). This compound is soluble in water (CRC Handbook of Chemistry & Physics, 1970-1971) and has been found in finished water (EPA, 1976).

II. METABOLISM

e-Caprolactam is excreted by rats partly as lactam and partly as e-amino acid. Rabbits metabolize e-caprolactam completely (Goldblatt *et al.*, 1954).

III. HEALTH ASPECTS

A. Observations In Man

Skin contact with caprolactam can cause serious burns if contact is prolonged and confined. Exposure in airborne dust at 5 mg/m³ causes skin irritation in some people but not at 1 mg/m³. Sensitivity has not been related to race, skin pigmentation, or other common indices of sensitivity (Ferguson and Wheeler, 1973). The prevalence of dermatoses among workers in a caprolactam manufacturing plant showed that contact dermatitis and eczema of the hands were most prevalent. Dry erythematous squamous foci on smooth skin was a typical manifestation (Dovshanskii *et al.*, 1972).

Light sensitivity of the eyes was produced by inhalation of caprolactam at 0.11 mg/m³ and higher. The olfactory threshold was 0.30 mg/m³. (Krichevskaya, 1968). An oral dose of 3 - 6 g was given daily for 3 - 5 years for the treatment of obesity in 90 subjects. No toxic effects were observed. There was no effect on appetite, and only one person developed an allergy to caprolactam (Anonymous, 1964).

B. Observations In Other Species

__Acute effects__. The acute lethal dosages in laboratory species are 500 - 900 mg/kg parenterally and over 1,000 mg/kg orally.

In dogs an intravenous injection of 0.003 g/kg increased arterial pressure; 0.1 g/kg caused a brief cardiac arrest and a sharp decrease in arterial pressure, and then an increase to a pressure well above normal. Additional results indicated an effect on the peripheral, as well as the central, nervous system (Polushkin, 1964).

__Chronic effects__. In a behavioral study with rats, ill-defined changes in conditioned-reflex activities were seen at a daily oral dose of 15 mg/kg for 2 months. In another chronic study (Statsek et al., 1976), guinea pigs were exposed to vapors of caprolactam (0.01-0.03 mg/liter) once every 2 days. On day 14 of the experiment, circulatory antibodies to caprolactam appeared. By day 30, serum antibodies were present in lung tissues; this suggested the development of a self-immunizing process.

__Mutagenicity__. No available data.

__Carcinogenicity__. No available data.

__Teratogenicity__. No available data.

__Reproduction__. Caprolactam at 120 - 150 mg/m^3 in air reduced rats' fecundity by causing heavy losses of embryos (Khadzhieva, 1969).

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity and long term oral toxicity of caprolactam, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

CARBON DISULFIDE

I. INTRODUCTION

Carbon disulfide is produced in petroleum and coal tar refining. Its principal uses are in the manufacture of rayon, rubber, chemicals, solvents, and pesticides (EPA, 1975d). United States production in 1973 was over 77 million pounds (USITC, 1975). It is soluble in water (0.294% at 20°C) (Merck Index, 1968). Carbon disulfide was detected in five of the 10 water supplies surveyed by the EPA (1975a).

II. METABOLISM

Absorption and elimination of carbon disulfide differs with species and route of administration. Most of the work on absorption and elimination has been related to inhalation toxicity. The little work with cutaneous exposure has shown a change in blood proteins and a change in zinc content (Brieger and Teisinger, 1967).

Carbon disulfide is 90% metabolized by the mixed-function oxidase enzyme system P-450 to inorganic sulfate (Dalvi et al., 1975). A portion of the sulfur released by carbon disulfide is thought to react with sulfide groups of cysteine residues in the microsomal protein to form hydrosulfide (Catignani and Neal, 1975). Small amounts of the compound (0.5%) are excreted as thiourea, 5-mercaptothiazolidone, and inorganic constituents in the urine (Teisinger, 1974). Some portion of the compound (8-10% is also excreted unchanged in the breath).

Inhalation-toxicity studies have shown that 10% of the carbon disulfide inhaled is exhaled unchanged. Of the remaining inhaled dose 70% is excreted as free or bound carbon disulfide and urinary sulfates, and 30% is stored in the body and slowly excreted as carbon disulfide and its metabolites.

Large concentrations of both free and bound carbon disulfide are found in the brain (guinea pig studies) and peripheral nerves (rat studies) of exposed animals. The ratio of bound to free carbon disulfide in the brain is 3:1. Blood and fatty tissues contain mainly bound carbon disulfide while the liver mainly free. Carbon disulfide can also chelate trace metals, especially copper and zinc.

III. HEALTH ASPECTS

A. Observations in Man

The effects of carbon disulfide inhalation have been examined in the light of their central nervous system and vascular effects on man. The lowest lethal concentration has been reported as 4,000 ppm in 30 m; in the same study, a person subjected to a concentration of 50 mg/m³ for 7 years had central nervous system effects (Registry of Toxic Effects of Chem. Substances, 1975). Moderate chronic exposure at less than 65 mg/m³ for several years has been reported by Cooper (1976) to cause polyneuropathy. In a study by Baranowska et al. (1966), humans have been shown to absorb 8.8 - 37.2 mg of carbon disulfide from an aqueous solution containing 0.33 - 1.67 g/liter. This was over a period of 1 h of hand-soaking.

The United States Occupational standards (TLV) recommends a maximum of 20 ppm. The standards allow a peak concentration of 100 ppm for 30 m in an 8-h period. The Union of Soviet Socialist Republics has set a standard of 4 ppm as the safe maximum, and the Czechoslovakians maintain 10 ppm as the safe limit (Hamilton and Hardy, 1974).

B. Observations in Other Species

Acute effects. The effects of acute administration of carbon disulfide have been examined in a variety of animals with a variety of routes of administration. Intraperitoneal injection of 400 mg/kg proved to be the lowest lethal dose in guinea pigs (Davidson and Feinlab, 1972). An intravenous LD$_{50}$ of 694 mg/kg in mice was reported by Hylin and Chin (1968).

In studies with subcutaneous injection, the LD$_{50}$ was 300 mg/kg in rabbits (Merck Index, Christensen and Luginbyhl, 1975); toxic effects have been observed at 1.7 mg/kg in rabbits (Okamoto, 1959). An LD$_{50}$ of 0.1 ml in mice was reported by Yudeles and Bessaiabova (1955). Rats showed toxic subcutaneous effects at 1 mg/kg (Okamoto, 1959). Oral administration of carbon disulfide in rats, produced toxic effects at 1 mg/kg (Freundt, et al., 1974a,b). Vinogradov (1966) showed that 1 ppm in the drinking water was nontoxic to rabbits; 70 ppm proved lethal.

Chronic effects. In a chronic study, Paterni et al. (1958) found that 6 mg/kg/day produced toxic effects in rabbits. The lowest lethal chronic dosage for rabbits was later shown to be 0.1 ml three times a week for 7 months (Michalova et al. 1959). Both of these studies used intramuscular administration of carbon disulfide.

In another study, carbon disulfide applied topically, produced a higher incidence of anemia in female than in male rats, and teratogenic effects were observed (Gut, 1969). When rats inhaled carbon disulfide at 10 mg/m^3, abnormalities of genitourinary and skeletal systems were found. Disturbances of ossification and blood formation and dystrophic changes in the liver and kidney were also noted (Bariliak _et al._, 1975).

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. Bariliak _et al._ (1975) showed that the inhalation of 10 mg/m^3 was lethal to embryos before and after implanation. Carbon disulfide at 2.2 g/m^3 for 4 h/day proved embyrotoxic if given to female rats during gestation and had no effect on male rats (Sal'nikova and Chirkova, 1974). Inhalation of lower concentrations (0.34 mg/liter for 210 days caused disturbances of estrus (Rosewiski _et al._, 1973). In a dominant-lethal test, inhalation of 10 mg/m^3 by male rats before copulation proved lethal to embryos (Bariliak _et al._, 1975).

IV. CONCLUSIONS AND RECOMMENDATIONS

Carbon disulfide has been demonstrated to produce distrubances in reproduction as well as teratogenic effects in animals when inhaled. There is no data availale on teratogenicity following oral exposure.

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity and long term oral toxicity of carbon disulfide, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

CARBON TETRACHLORIDE

I. INTRODUCTION

Over 1 billion pounds of carbon tetrachloride (tetrachloromethane) was produced in the United States in 1973 (USITC, 1975). It is used mostly in the manufacture of chlorofluoromethanes, but also in grain fumigants, fire extinguishers, solvents, and cleaning agents.

Carbon tetrachloride is highly persistent and insoluble in water. Carbon tetrachloride was identified in District of Columbia drinking water at 5 μg/liter (Schneiman _et al._, 1974). The EPA's 80-city survey showed that it was detected in 10 locations in trace amounts, at 3 μg/liter or less (EPA, 1975a). The survey of 10 water utilities showed that it was present in eight supplies. The Region V survey of 83 water supplies indicated that carbon tetrachloride is not formed during chlorination water treatment (EPA, 1975b).

II. METABOLISM

Carbon tetrachloride in rats and humans is rapidly absorbed and distributed and is excreted primarily through the lungs. The excretion products are 85% parent compound, 10% carbon dioxide, and smaller quantities of other products, including chloroform. In animal studies, chloroform, hexachloroethane, and two unidentified metabolites were found in rabbits. The mechanism of metabolism is postulated as a free-radical pathway (Paul and Rubinstein, 1963; Butler, 1961; Fowler, 1969; Hathway, 1974; Recknagel, 1967).

III. HEALTH ASPECTS

A. Observations in Man

Carbon tetrachloride is readily absorbed from the gastrointestinal tract and by inhalation through the lungs. A fatal dose for children has been reported as low as 3 ml, but there is great variation in individual susceptibility. Intestinal absorption is enhanced by fats, oils and alcohol. (Masoud _et al._, 1973).

Some persons exposed to carbon tetrachloride will develop severe liver damage with little or no evidence of renal involvement while others will present with renal shutdown and no hepatic disease. The reasons for this are not known (Eckardt, 1965).

In eight instances of either acute or subacute carbon tetrachloride poisoning seven patients suffered renal insufficiency and six of these required dialysis. Two died from heart failure. None of the six survivors showed any evidence of liver damage (Dume *et al.*, 1969).

Following a large acute exposure the primary finding is of centrilobular necrosis. If exposure is not too massive repair may begin after 3 or 4 days and be complete in three weeks. Chronic exposure usually results chiefly in symptoms of gastrointestinal upset such as nausea and vomiting, and nervous system symptoms such as headache, drowsiness, and excessive fatigue. It is rare to find jaundice following either acute or chronic exposure (Browning, 1961).

Gastric symptoms have been reported following chronic inhalation of from 45 - 100 ppm carbon tetrachloride. When exposure is from 100 - 300 ppm the symptoms in addition to gastrointestinal upset include apathy or mental confusion and weight loss (Lewis, 1961).

B. Observations in other Species

Acute effects. Oral LD_{50} values are 6.4 (5.4-7.6) ml/kg in young male Wistar rats (McLean and McLean, 1966) 4.73 (4.16-5.38) ml/kg in mature male Sprague-Dawley rats (Pound *et al.*, 1973) and 1.5 ml/kg in male and female mongrel dogs (Klaassen and Plaa, 1967). The intraperitoneal LD_{50} is 2.23 ml/kg in rats (Maling *et al.*, 1974). Toxicity indexes have been set up for both animals and man. Signs and symptoms of toxicity include dyspnea, cyanosis, proteinuria, hematuria, jaundice, hepatomegaly, optic neuritis, ventricular fibrillation, eye-nose-throat irritation, headache, dizziness, nausea, vomiting, abdominal cramps, and diarrhea.

Chronic effects. Biochemical and biologic lesions include hepatic cirrhosis and necrosis, renal damage, changes in blood enzymes (serum glutamic pyruvic transaminase and alkaline phosphatase), and increased serum bilirubin (Busuttil *et al.*, 1972, Litchfield and Gartland, 1974).

A variety of interactions have been described to relate carbon tetrachloride exposure to metabolic inhibitors and inducers and diet. Many studies have reported reduction or potentiation of toxicity indexes, including liver necrosis-cirrhosis and blood enzyme changes (McLean and McLean, 1966; Maling *et al.*, 1974; Marawill and Gornall, 1952; Cawthorne *et al.*, 1970 Traiger and Plaa, 1971; Litterst *et al.*, 1973).

Mutagenicity. Carbon tetrachloride was negative in a host-mediated assay using NMRI mice and strains G46 and TA1950 of *Salmonella typhimurium his* (Braun and Schoneich, 1975). Carbon tetrachloride was also negative in an *in vitro* *Salmonella*/microsome mutagenicity assay (McCann *et al*., 1975).

Carcinogenicity. In a series of studies of the carcinogenic potential of carbon tetrachloride, hepatomas were found in mice, hamsters, and rats after administration by several routes, including oral. There was, however, no evidence of tumors in other organs within the time limits of the experiment (usually less than life span). The tumor response depended on both the dosage and the interval between doses. With intermittent exposure, it was found that total dose and duration were more important than the dosage (IARC, 1972; Murphy, 1975).

In a study with mice, oral administration of 0.1 ml twice a week for 20-26 weeks produced hepatomas that were interpreted by the investigators as indicative of focal nodular hyperplasia, not neoplasia (Confer and Stenger, 1965). Kawasaki (1965) reported that 0.2 - 0.3 ml/100 g injected subcutaneously every 2 weeks produced a low number of hepatomas in Wistar rats. A 1.3 ml/kg oral dose twice a week for 12 weeks in Buffalo rats was reported to cause cholangiofibrosis from proliferating bile ducts (Reuber and Glover, 1967). Oral administration to Syrian golden hamsters at 6.25 - 12.5 µl once a week for 30 weeks followed by 25 additional weeks of observation induced liver cell carcinomas associated with postnecrotic cirrhosis and regenerative hyperplastic nodules (Della-Porta *et al*., 1961).

Teratogenicity. No teratogenic effects were seen when carbontetrachloride was administered to rats (Wilson, 1954).

IV. CARCINOGENIC RISK ESTIMATE

Carbon tetrachloride has been given orally in a number of studies with mice, rats, hamsters, and dogs (IARC, 1972). It has also been used as a positive control in cancer bioassays (NCI, 1976). In the trichloroethylene study, the carbon tetrachloride positive control produced much higher incidences of hepatocellular carcinomas than did trichloroethylene.

The available sets of dose response data from the NCI trichloroethylene bioassay were individually considered as described in the risk section in the chapter on margin of safety. Each set of dose response data was used to statistically estimate both the life-time risk and an upper 95% confidence bound on the life-time risk at the low dose level. These estimates are of life-time human risks and have been corrected for species conversion on a dose per surface area basis. The risk estimates are expressed as a probability of cancer after a life-time consumption of 1 liter of water per day containing Q ppb of the compound of interest. For example, a risk of $1X10^{-6}Q$ implies a life-time probability of $2X10^{-5}$ of cancer if 2 liters per day were consumed and the concentration of the carcinogen was 10 ppb (i.e. Q=10). This means that at a concentration of 10 ppb during a lifetime of exposure this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the United States is taken to be 220 million people this translates into 4,400 excess lifetime deaths from cancer or 62.8 per year. Since several data sets are typically available the range of the low dose risk estimates are reported. For carbon tetrachloride at a concentration of 1 μg/liter (Q=1) the projected risk for man would fall between $4.5-5.4X10^{-8}Q$. The upper 95% confidence estimate of risk at the same concentration would be from $1.1 - 1.8X10^{-7}$ Q.

V. CONCLUSIONS AND RECOMMENDATIONS

The acute-toxicity effects of carbon tetrachloride are best characterized as hepatic nodular hyperplasia and cirrhosis and renal dysfunction in both experimental animals and man. It had no mutagenic potential in *in vitro* and *in vivo* test systems. Its teratogenic potential has not been firmly established. Carcinogenic bioassays have produced hepatomas in mice, rats, and hamsters, associated in most cases with regenerative nodular hyperplasia or postnecrotic cirrhosis.

In light of the above and taking into account the risk projections it is suggested that very strict criteria be applied when limits for carbon tetrachloride in drinking water are established. The available chronic toxicity data are summarized in Table VI-47.

TABLE VI-47. Summary of Chronic Toxicity Data for Carbon Tetrachloride

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse-effect level or lowest Minimal-effect level	Effect Measured	Reference
Mouse	20-26 wks.		0.1 ml, twice a week (oral)	Nodular hyperplasia	Confer & Stenger, 1965
Rat	12 wks.		1.3 ml/kg twice a week (oral)	Cholangiofibrosis	Reuber & Glover, 1967
Rat (Male)	78 wks.	0,47,94 mg/kg/day 50 animals/group	47 mg/kg/day (oral)	Hepatomas	NCI, 1976
Rat (Female)	78 wks.	0,80,159 mg/kg/day 49 animals/group	80 mg/kg/day (oral)	Hepatomas	NCI, 1976
Hamster	30 wks.	6.25-12.5 µl/week 20 animals	6.25 µl/week (oral)	Hepatomas	Della-Porta *et al.*, 1961

[This compound is an animal carcinogen]

CHLORAL

I. INTRODUCTION

Chloral (trichloroacetaldehyde) is used in spraying and pouring of polyurethanes. Chloral is very soluble in water. It has been identified in six of the ten water supplies surveyed by EPA (1975a) at 5 μg/liter in the finished water of Philadelphia, 3.5 μg/liter in Seattle, and 2 μg/liter in Cincinnati (EPA, 1975a).

II. METABOLISM

Chloral is metabolized in man by alcohol dehydrogenase to trichloroethanol. This NADH dependent reduction takes place in the liver and is accelerated by ethanol which regenerates NADH. Small amounts of chloral are metabolized to trichloroacetic acid. Trichloroethanol is excreted mainly in the urine as a conjugate of glucuronic acid (Goodman and Gilman, 1975).

III. HEALTH ASPECTS

A. Observations in Man

Chloral has been used extensively as a hypnotic in its hydrated form, chloral hydrate, which is more stable. It is quite irritating to skin and mucous membranes. A toxic oral dose for adults is approximately 10 g although death has been reported from 4 g. Therapeutic doses (.5-1.0 g) produce hypnosis through its central depressant activity as well as such unpleasant effects as epigastric distress, nausea, vomiting, lightheadedness, malaise, ataxia, and nightmares. An overdose of the compound can cause respiratory and cardiac effects. Chloral hydrate interacts with ethanol to increase skin temperature and heart rate and to inhibit motor reflexes (Goodman and Gilman, 1975).

Some European reports have set a maximal permissible concentration of 0.2 mg/liter (Stoefen, 1973).

B. Observations in Other Species

Acute effects. Acute oral LD_{50} values of chloral have been established as 285 mg/kg in rats, 1,100 mg/kg in mice, and 1,000 mg/kg in dogs. In an acute inhalation study, chloral hydrate at 0.06 mg/liter of air lowered growth rate in mice; some leukocytosis and decreased albumin:globulin ratios were observed (Boitsov et al., 1970). Chloral given to rats at 1 mg/kg altered concentrations of hemoblobin, serum cholesterol, and transaminases and decreased bromsulphalein retention (Kryatov, 1970).

Chloral has been reported to increase plasma prolactin content in rats. Its metabolite, chloral hydrate, inhibits protein synthesis *in vivo* and has been shown to block the metaphase in segmenting eggs, with some alteration in chromosomal structure.

Chronic effects. No available data.

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity, and long term oral toxicity of chloral, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

CHLOROBENZENE

I. INTRODUCTION

Chlorobenzene (Monochlorobenzene) is used in the manufacture of aniline, insecticides, phenol, and chloronitrobenzene and as an intermediate in the manufacture of dyestuffs (EPA, 1975d). The United States production of chlorobenzene in 1973 was over 397 million pounds (USITC, 1975). During chlorination water treatment, chlorobenzene may be formed. It is insoluble in water (CRC Handbook of Chemistry and Physics, 1970-1971). Finished water in nine of the 10 water supplies surveyed by the EPA (1975a) contained chlorobenzene, with 5.6 μg/liter in Terrebonne Parrish, Louisianna, and 4.7 μg/liter in New York City.

II. METABOLISM

Although many foreign chemicals are metabolized to inactive substances, chlorobenzene appears to be converted to a metabolite that can produce tissue damage. This damage may be blocked by prior administration of piperonyl butoxide. The metabolite is apparently produced in the liver and transported to the kidneys by the circulation. Pretreatment of rats with phenobarbital increases the liver toxicity of chlorobenzene (Reid, 1973). Chlorobenzene may be metabolized to p-(p-chlorophenyl)mercapturic acid by several steps (Norton, 1975). The hepatotoxic metabolite may be an epoxide excreted in the bile, reabsorbed, and finally excreted by the kidneys.

III. HEALTH ASPECTS

A. Observations in Man

Chlorobenzene is irritating to the respiratory system and is a central nervous system depressant. The Union of Soviet Socialist Republics has suggested 0.02 mg/liter as the maximal permissible concentration in drinking water (Stoefen, 1973). This was based on odor and taste.

B. Observations in Other Species

Acute effects. Chlorobenzene has an acute oral LD_{50} of 2,910 mg/kg in rats (Toxic Substances List, 1974).

Chronic effects. The no-effect dosage in rats after 7 months of administration was 0.001 mg/kg/day (Varshavskaya, 1968). Other studies have shown no-effect oral dosages of 54.5 mg/kg in dogs and 12.5 mg/kg in rats (Knapp *et al.*, 1971).

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity, and long term oral toxicity of chlorobenzene, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

BIS(2-CHLOROETHYL)ETHER

I. INTRODUCTION

bis(2-Chloroethyl)ether (dichloroethyl ether) is used as a soil fumigant; as an insecticide and acaricide; as a solvent for fats, waxes, greases, and cellulose esters; as a scouring agent for textiles; in paints, varnishes, and lacquers; as a paint remover; in dry cleaning; and in the manufacture of medicinals and pharmaceuticals (EPA, 1975d).

bis(2-Chloroethyl)ether is moderately persistent and insoluble in water. It can be formed during chlorination of water treatment when ethyl ether is present. *bis*(2-Chloroethyl)ether has been identified in finished water at 0.5 µg/liter in Philadelphia and 0.44 µg/liter in New Orleans (EPA, 1975a,c).

II. METABOLISM

No data are available on the metabolism, absorption, or excretion of *bis*(2-Chloroethyl)ether.

III. HEALTH ASPECTS

A. Observations in Man

Shrenk *et al.* (1933) exposed humans to *bis*(2-Chloroethyl)ether and found that a concentration of 550 ppm was intolerable and caused irritation of the eyes and nasal passages. Concentrations of 100 ppm and 260 ppm were irritating, but tolerable; at 35 ppm, there was no irritation, but a nauseous odor persisted.

B. Observations in Other Species

Acute effects. The oral LD_{50} has been given as 75 - 150 mg/kg in rats (Smyth and Carpenter, 1948; Spector, 1956; Hake and Rowe, 1963) and 136 mg/kg and 126 mg/kg in mice and rabbits, respectively (Spector, 1956). The cutaneous LD_{50} was 410 mg/kg (Spector, 1956) and 90 mg/kg (Hake and Rowe, 1963) in rabbits and 0.3 ml/kg in guinea pigs (Smyth and Carpenter, 1948). Smyth and Carpenter (1948) reported that the material caused moderate to severe irritation to rabbits' eyes, but that apparent healing occurred within 24 h. They also exposed six rats to 1,000 ppm for 45 m. Three of the rats died within 14 days. In another inhalation study in rats (Carpenter *et al.*, 1949), exposure at 250 ppm for 4 h killed some exposed rats. In guinea pigs, 500-1,000 ppm produced immediate severe eye and nasal irritation, and exposure for 1.5-3 h caused respiratory disturbances and deaths with pulmonary lesions (Shrenk, 1933).

Chronic effects. In chronic studies, rats and guinea pigs were exposed to *bis*(2-Chloroethyl)ether at an average of 414 mg/m³ for 2 h/day, 5 days/w, for 93 exposures during 130 days. No serious injury and only mild physiologic stress were noted (Hake and Rowe, 1963).

Mutagenicity. No available data.

Carcinogenicity. Berenblum (1935) painted a 1.0% solution in acetone on mice for 15 weeks and found no irritation. Van Duuren *et al.* (1972) applied *bis*(2-Chloroethyl)ether in benzene once to mouse skin as an initiator and then applied phorbol myristate three times a week for 590 days. The compound did not show tumor-initiating activity. The same authors reported the development of sarcomas at two sites of injection out of 30 mice receiving one 1.0-mg subcutaneous injection of *bis*(2-Chloroethyl)ether per week for their life spans. Seventy two mice were given oral *bis*(2-Chloroethyl)ether at 100 mg/kg/day from week 7 - 28 of life. Afterwards, 300 ppm was fed in the diet until the age of 80 weeks. Male mice of two strains and the females of one strain had an increased incidence of hepatomas (Innes *et al.*, 1969). In another study rats were given 50 mg/kg and 25 mg/kg by intubation three times per week for 18 months and followed for 6 months. The compound was not carcinogenic (Weisburger *et al.*, 1973).

Teratogenicity. No available data.

IV. CARCINOGENIC RISK ESTIMATES.

bis(2-Chloroethyl)ether has produced dose related hepatomas when given orally to mice (Innes *et al.*, 1969). The female mice of one strain did not develop any hepatomas. The available sets of dose response data were individually considered as described in the risk section in the chapter on margin of safety. Each set of dose response data was used to statistically estimate both the life-time risk and an upper 95% confidence bound on the life-time risk at the low dose level. These estimates are of life-time human risks and have been corrected for species conversion on a dose per surface area basis. The risk estimates are expressed as a probability of cancer after a life-time consumption of 1 liter of water per day containing Q ppb of the compound of interest. For example a risk of $1X10^{-6}$ Q implies a life-time probability of $2X10^{-5}$ of cancer if 2 liters per day were consumed and the concentration of the carcinogen was 10 ppb (i.e. Q=10). This means that at a concentration of 10 ppb during a lifetime of exposure this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the United States is taken to be 220 million people this translates into 4,400 excess lifetime deaths from cancer or 62.8 per year. For bis(2-chloroethyl)ether at a concentration of 1 µg/liter (Q=1) the estimated risk for both sexes is $8.1\times10^{-7}Q$. The upper 95% confidence estimate is $1.2\times10^{-6}Q$.

V. CONCLUSIONS AND RECOMMENDATIONS

Even though the acute and chronic effects of bis(2-chloroethyl)ether have not been fully established it has been shown to produce dose-related tumors when given orally to mice.

In view of this potential in humans and taking into account the risk estimates it is suggested that very strict criteria be applied when limits for bis(2-chloroethyl)ether in drinking water are established.

The available chronic toxicity data are summarized in Table VI-48.

TABLE VI-48. Summary of Chronic

Toxicity Data for Bis(2-Chloroethyl)Ether

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse-effect Level or lowest Minimal-effect Level	Effect Measured	Reference
Rat	130 days		414 mg/m^3 (Inhalation)	mild physiologic stress	Hake & Rowe, 1963
Mouse	80 wks.	0-100 mg/kg/day	100 mg/kg/day (oral)	Hepatomas	Innes *et al*., 1969

[This compound is a suspected animal carcinogen]

CHLOROFORM

I. INTRODUCTION

The chief uses (96%) of chloroform, or trichloromethane (after conversion to chlorodifluoromethane), in the United States since 1970 have been as a refrigerant and aerosol propellant and in the synthesis of fluorinated resins. The remainder has been used as an industrial solvent, as a heat-transfer medium in fire extinguishers (with carbon tetrachloride), and as a pesticide (IARC, 1972) and was used directly in pharmaceuticals and toiletries. The FDA has issued final regulations to ban chloroform as an ingredient in any human drugs or cosmetic products effective July 29, 1976 (FR Vol. 41, No. 125, June 1976). The United States production of chloroform in 1973 was over 250 million pounds (USITC, 1975).

Chloroform is not biodegradable in water. Its solubility is 1 ml/200 ml of water at 25°C (Merck Index, 1968). Chloroform is produced during chlorination water treatment. The recent EPA water-supply surveys of finished chlorinated drinking water indicated that 95-100% of the finished waters surveyed contained chloroform. The mean concentration was 20 µg/liter; the highest was 311 µg/liter, in Miami (EPA, 1975a,b).

II. METABOLISM

Chloroform is rapidly absorbed, distributed throughout body fat depots and tissues, and excreted rapidly in mice, rats and humans. It is metabolized in part to carbon dioxide and methylene chloride. Free-radical formation is postulated from enzymatic degradation of the carbon-halogen bond, to account for hepatic damage. Inhibitors and activators of metabolizing enzymes have been found to alter tissue binding and subsequent renal and hepatic necrosis (Van Poznak, 1976; Cascorbi, 1971; Paul and Rubinstein, 1963; Fry *et al.*, 1972; Butler, 1961; Ilett *et al.*, 1973; Brown *et al.*, 1974).

III. HEALTH ASPECTS

A. Observations In Man

In a chronic clinical study, dentifrice containing 3.4% chloroform and mouthwash with 0.43% chloroform were given to subjects for 1 - 5 years. The estimated daily ingestion was 0.1 - 0.96 mg/kg; no hepatotoxicity was observed (DeSalva *et al.*, 1975). In a 10-year clinical study, daily ingestion of 1.6 - 2.6 g of chloroform in a cough suppressant, roughly equivalent to 23 - 37 mg/kg/day, resulted in some reversible hepatotoxicity (Wallace, 1950).

The NIOSH(1974) recommended the occupational exposure to chloroform at not in excess of 10 ppm determined as time-weighted average exposure for up to a 10 h workday.

B. Observations In Other Species

Acute effects. Oral LD_{50} values have been calculated for a variety of experimental animals: 0.8 (0.7-0.9), 0.9 (0.8-1.1), and 0.3 (0.2-0.5) ml/kg in Sprague-Dawley male rats weighing 300-470 g, males weighing 80-160 g, and males and females weighing 16-50 g, respectively (Kimura et al., 1971); 0.33 (0.26-0.40), 0.20 (0.16-0.24), and 0.08 (0.07-0.10) ml/kg in male C5Bl/6, B6D2F1/J, and DBA/2J mice, respectively (Hill et al., 1975); and 1.0 ml/kg in male and female dogs. The intraperitoneal LD_{50} was 1.2 (1.0-1.3) ml/kg in male Swiss-Webster mice weighing 25-35 g (Klaassen and Plaa, 1966).

Mutagenicity. No available data.

Carcinogenicity. The carcinogenic effects of chloroform have been examined in mice and rats. A- strain mice were orally dosed with 0.1 - 1.6 ml/kg every 4 days for 30 doses. All experimental females survived, but hepatoma associated with liver necrosis was produced at 0.4 ml/kg. Of the five experimental males, three survived. Of the survivors, none had hepatoma or liver necrosis at 0.2 ml/kg, but 0.1 ml/kg induced kidney necrosis in males and not in females (Eschenbrenner, 1945).

In another study, $B6C3F_1$ strain male and female mice were given oral doses of chloroform at 138 or 277 mg/kg and 238 or 477 mg/kg, respectively, five times a week for 78 weeks. Animals were sacrificed at 92-93 weeks; hepatocellular carcinoma was observed in all groups. Nodular hyperplasia was found in low-dosage males without carcinomas. In male and female Osborne-Mendel rats, chloroform at 90 or 180 mg/kg in males and 100 or 200 mg/kg in females five times a week for 78 weeks produced kidney epithelial tumors; 24% occurred in high-dosage males and 8% in low-dosage males. Benign thyroid tumors were seen in the females (NCI, 1976).

Teratogenicity. In a study to examine the teratogenicity of oral chloroform in rats and rabbits, subjects were given 20, 50, or 126 mg/kg on days 6 - 18 of gestation. Although there was no evidence of teratogenicity, offspring of both species had reduced weights (Thompson et al., 1974).

IV. CARCINOGENIC RISK ESTIMATES

In a recent study conducted by the National Cancer Institute (NCI) (1976), chloroform was administered to rats and mice orally in corn oil by gavage. Dose-response relationships were found for epithelial tumors of the kidneys and renal pelvis in the rats and hepatocellular carcinomas in the mice. The estimated risks for the mice and the rats were comparable within an order of magnitude.

A study by Roe (1976) also reported an increased incidence of hepatocellular carcinoma in female rats and in one strain of male mice when dosed orally ith chloroform. When this data is extrapolated along with the NCI data the risk estimates are remarkably consistent.

The available sets of dose response data (Roe, 1976; NCI, 1976) were individually considered as described in the risk section in the chapter on margin of safety. Each set of dose response data was used to statistically estimate both the life-time risk and an upper 95% confidence bound on the life-time risk at the low dose level. These estimates are of life-time human risks and have been corrected for species conversion on a dose per surface area basis. The risk estimates are expressed as a probability of cancer after a life-time consumption of 1 liter of water per day containing Q/ppb of the compound of interest. For example a risk of $1X10^{-6}$ Q implies a life-time probability of $2X10^{-5}$ of cancer if 2 liters per day were consumed and the concentration of the carcinogen was 10 ppb (i.e., Q=10). This means that at a concentration of 10 ppb during a lifetime of exposure this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the United States is taken to be 220 million people this translates into 4,400 excess lifetime deaths from cancer or 62.8 per year. Since several data sets are typically available the range of the low dose risk estimates are reported. For chloroform at a concentration of 1 µg/liter (Q=1) the estimated risk for man would fall between $1.5-3.0X10^{-7}$Q. The upper 95% confidence estimate of risk at the same concentration would fall between $3.7-7.5X10^{-7}$Q.

V. CONCLUSIONS AND RECOMMENDATIONS

Acute toxicity of chloroform to experimental animals and man is characterized by hepatic and renal lesions and damage, including necrosis and cirrhosis. This material, although highly embryotoxic, is apparently not highly teratogenic. Mutagenicity studies were not found in the literature. A carcinogenicity bioassay in mice demonstrated hepatomas in one study that were associated with liver necrosis; the number of animals used in each group was not adequate for statistical analysis. In a recent study with mice and rats, hepatocellular carcinomas and hepatic nodular hyperplasia were observed in both male and female mice, whereas kidney epithelial tumors were seen only in male rats. Data strongly support the contention that chloroform is carcinogenic in at least one strain of mouse and one strain of rat.

In light of the above and taking into account the risk projections, it is suggested that strict criteria be applied when limits for chloroform in drinking water are established.

The available chronic toxicity data are summarized in Table VI-49.

TABLE VI-49. Summary of Chronic Toxicity Data for Chloroform

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse-effect level or lowest Minimal-effect Level	Effect Measured	Reference
Mouse	96 wks.	0,17,60 mg/kg/day 35-38 animals/group	60 mg/kg/day (oral)	Renal tumors	Roe, 1976
Mouse	96 wks.	0,17,60 mg/kg day 35-38 animals/group	17 mg/kg/day (oral)	Liver tumors	Roe, 1976
Rat	96 wks.	0,60 mg/kg/day 49 animals/group	60 mg/kg/day (oral)	Total tumors	Roe, 1976
Rat	life time	0,90,180 mg/kg/day 50 animals/group	90 mg/kg/day (oral)	Kidney tumors	NCI, 1976

[This compound is an animal carcinogen]

CYANOGEN CHLORIDE

I. INTRODUCTION

Cyanogen chloride (chlorine cyanide) is used in organic synthesis, tear gas, and fumigant gases. It is soluble in water (CRC Handbook of Chemistry and Physics, 1970-1971) and has been detected in the finished water of eight of the 10 water supplies surveyed by the EPA (NORS, EPA 1975a).

II. METABOLISM

An *in vitro* study by Aldridge (1951) on cyanogen chloride metabolism in rat blood showed that hemoglobin and glutathione rapidly metabolise cyanogen chloride to cyanide. The glutathione is the key metabolising agent. Hemoglobin transforms cyanogen chloride to a compound that is later metabolized by glutathione, to liberate cyanide (Aldridge, 1951). Although red cells convert cyanogen chloride to hydrogen cyanide, serum decomposes cyanogen chloride without producing hydrogen cyanide. The toxicity of cyanogen chloride is due to the formation of hydrogen cyanide (Aldridge and Evans, 1946).

II. HEALTH ASPECTS

A. Observations in Man

The effects of the inhalation of cyanogen chloride in man were examined in two studies by Flury (1931, 1941). It was found that the lowest lethal concentration (LC_{50}) was 48 ppm, and the lowest irritant concentration, 1 ppm.

B. Observations in Other Species

Acute effects. The effects of acute cyanogen chloride inhalation have also been examined in a series of experimental animals. The LC_{50}'s have been reported as follows: in rats, 118 ppm in 30 m; in mice, 177 ppm in 30 m; in guinea pigs, 207 ppm in 30 m; in rabbits, 207 ppm in 30 m (Registry of Toxic Effects of Chem. Substances, 1975); in goats, 1.8 ppm in 2 m; in dogs, 48 ppm in 6 h; and in cats, 40 ppm in 18 m (Flury and Zernick 1931). The intravenous administration of cyanogen chloride in rats yielded an LD_{50} of 4.0 mg/kg (Leitch and Bauer, 1945). Subcutaneous administration of the compound in mice, dogs, and rabbits yielded LD_{50} values of 39, 5, and 20 mg/kg, respectively (Registry of Toxic Effects of Chem. Substances, 1975). The oral acute LD_{50} in rats was 6.0 mg/kg (Leitch and Bauer, 1945). Allen *et al.* (1948) studied the formation of cyanogen chloride by chlorination of sewage effluent; the threshold concentration for toxicity to fish at 17 - 22°C was 0.08 ppm.

The effects of subchronic, oral administration of cyanogen chloride in drinking water were examined in mice. Although 1 week of exposure produced no weight loss, one death was observed on the first day (National Defense Research Committee, 1943).

Chronic effects. No available data.

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

The acute toxicity of cyanide is well known, but the chronic toxicity has been less studied.

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity, and long term oral toxicity of cyanogen chloride, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

Di-*n*-BUTYLPHTHALATE

I. INTRODUCTION

Di-*n*-butylphthalate (DBP) is used in the manufacture of plasticizers, plastics, and in cosmetics, explosives, solid rocket propellant, textile lubricating agents, safety glass, insecticides, printing inks, paper coatings, and adhesive (EPA, 1975d). The United States production of di-*n*-butylphthalate in 1973 was about 30 million pounds (USITC, 1975).

This compound is insoluble in water (CRC Handbook of Chemistry & Physics, 1970-1971) and very persistent in the environment (EPA, 1975d). Six of the 10 water supplies surveyed by the EPA (1975a) contained di-*n*-butyl phthalate; the highest concentration was 5 μg/liter in Miami.

II. METABOLISM

Williams (1959) suggested that di-*n*-butylphthalate is one of the phthalate esters likely to be hydrolysed *in vivo*, yielding phthalic acid and an alcohol. No accumulation of dibutylphthalate or monobutylphthalate was found by Williams and Blanchfield (1975) in tissues of rats fed di-*n*-butylphthalate at 1 g/kg of feed for 12 weeks. These authors reported that 80-90% of a dose of (^{14}C)di-*n*-butylphthalate was metabolized and excreted in the urine in 48 h. Phthalic acid, monobutyl phthalate, mono(3-hydroxybutyl)phthalic acid, and mono (4-hydroxybutyl)phthalate were found in the urine. Smith (1953) found that DBP was hydrolysed *in vitro* by pancreatic lipases; this suggested that it is metabolized like fat that is normally in the diet.

III. HEALTH ASPECTS

A. Observations in Man

Fairhall (1957) reviewed a report of an accidental ingestion of 10 g of DBP. Hours after ingestion, the patient was nauseous and giddy. His eyes were inflamed and painful, with photophobia and lacrimation. Toxic nephritis occurred, and his urine contained red and white cells and albumin. The patient recovered fully.

B. Observations in Other Species

Acute effects. Di-n-butylphthalate has low acute and chronic toxicity. The single-dose oral LD_{50} in animals is reported to be 9 g/kg (Smith, 1953) and 12.5 g/kg (Nikonorow *et al*., 1973). The intraperitoneal LD_{50} is reported to be 6.75-8.0 g/kg in mice (Hodge *et al*., 1942; Karel *et al*., 1947; Calley *et al*., 1966).

Chronic effects. Smith (1953) fed rats a diet of 1.25% DBP for a year. The dose was 1,600 mg/kg at the start and 525 mg/kg at termination. Half the rats died in the first week; those sacrificed at a year had no specific gross or microscopic pathologic effects. Nikonorow *et al*. (1973) fed rats 0.125% of DPB in the diet for a year and recorded six deaths in the 40 rats, compared with four in 40 untreated control rats. Daily intubation of 0.12 g/kg and 1.20 g/kg for 3 months produced only a single death at the high dosage in rats (Piekacz, 1971a). Both dosages were reported, however, to produce enlargement of the liver. Shibko and Blumenthal (1973) reported no effects in dogs given 18 mg/kg/day for a year.

Mutagenicity. No available data.

Carcinogenicity. No chronic studies with animals have revealed signs of carcinogenesis at the time of death.

Teratogenicity. Teratogenic effects of DBP were identified in a study by Singh *et al*. (1972a). Rats were given one-tenth, one-fifth, and one-third of the LD_{50} (3.2 g/kg) intraperitoneally on day 5, 10, or 15 of gestation. Partially dose-related resorption and a 20 - 30% incidence of skeletal abnormalities were found at the high dosage. Studies by Bower *et al*. (1970) in chicken eggs showed 79% mortality at 0.1 ml, 67% at 0.05 ml, compared with 47% for the oil controls.

Reproduction. Reproduction studies reported by Piekacz (1971b) included treating female rats with DBP at 0.60 and 0.12 mg/kg for 3 months before mating. The low dosage produced two resorptions, the high dosage 22, and the controls four. Piekacz (1971b) also gave rats DBP orally daily at 1% or 5% of the LD_{50} for 12 weeks. The numbers of fetuses and resorption sites were statistically different in the 5% goup as compared to the controls. Other groups of 10 rats were intubated daily with 1% and 5% of the LD_{50} during pregnancy. The number of fetuses was reduced, and resorptions increased. DBP had a greater adverse effect than di(2-ethylhexyl)phthalate, with which it was compared.

IV. CONCLUSIONS AND RECOMMENDATIONS

The major effect of di-n-butylphthalate in animals involves disturbances in reproduction and teratogenicity. There is no data available on mutagenicity and the chronic feeding studies did not show any carcinogenesis.

An ADI was calculated on the basis of the chronic toxicity data. Based on these data the ADI is 0.11 mg/kg/day. The calculations and available chronic toxicity data are summarized in Table VI-50.

TABLE VI-50. Summary of Chronic Toxicity Data for di-n-Butyl-Phthalate

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse-effect Level or Lowest Minimal-effect Level	Effect Measured	Reference
Rat	1 yr.	0-525 mg/kg/day, 10 animals per group	110 mg/kg/day[c] (oral)	No adverse effect	Smith, 1953
Rat	1 yr.	0,0.125%, 40 animals per group	0.125 % (oral)	No adverse effect	Nikonorov *et al.*, 1973

Using an uncertainty factor of 1,000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{110}{1,000} = 0.11 \text{ mg/kg/day (ADI)},\ 0.11 \times 70^{a} \times 0.1^{b} = 0.77 \text{ mg/liter}$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Test study from which to calculate suggested no-adverse effect level.

1,2-DICHLOROETHANE

I. INTRODUCTION

1,2-Dichloroethane (ethylene dichloride) is used in the manufacture of vinyl chloride and tetraethyl lead; as an insecticidal fumigant; in tobacco flavoring; as a constituent of paint, varnish, and finish removers; as a metal degreaser; in soap and scouring compounds; in wetting and penetrating agents; and in chemical synthesis and ore flotation (EPA, 1975d). The United States production was over 9 billion pounds in 1973 (USITC, 1975).

1,2-Dichloroethane is difficult to degrade biologically. It is soluble in about 120 parts of water (Merck Index, 1968). The Region V survey of 83 water supplies concluded that it is not produced during chlorination of water. The survey also indicated that 13% of the finished water contained 1,2-dichloroethane, at a mean concentration of 1 μg/liter (EPA, 1975b). Of the 80 water supplies surveyed in 1974, 26 contained 1,2-dichloroethane, at less than 0.2 to 6 μg/liter (EPA, 1975a). A concentration of 8 μg/liter has been reported in New Orleans finished water (EPA, 1974).

II. METABOLISM

1,2-Dichloroethane is rapidly absorbed after oral or pulmonary exposure (Morgan et al., 1970). It is metabolized in mice by enzymatic dehalogenation and oxidation through the 2-chloroethanol intermediate to the chloroacetic acid excretion product (Yllner, 1971). Both enzymatic dehalogenation and oxidation appear to take place in the liver (Morgan et al., 1970). The principle target organs in mice are the liver, kidneys, and adrenals (Plaa and Larson, 1965).

III. HEALTH ASPECTS

A. Observations in Man

In man, exposure to high vapor concentrations of 1,2-dichloroethane results in irritation of the eyes, nose, and throat. Continued or repeated exposure to concentrations above the response threshold produce central nervous system depression and injury to the liver, kidneys, and adrenals (American Nat. Standards Inst., 1970; AIHA, 1955, 1965). The accidental oral ingestion of a single dose of 0.5 - 1.0 g/kg has been reported to result in death; autopsy revealed liver necrosis and focal adrenal degeneration and necrosis (Wirtschafter and Schwartz, 1939; Yodaiken and Babcock, 1973).

B. Observations in Other Species

Acute effects. The acute oral LD$_{50}$ of 1,2-dichloroethane has been established at 0.77 (0.67-0.89) ml/kg in rats (Smyth et al., 1969). LC$_{50}$ values for vapor inhalation are 12,000 ppm in 0.53 h, 3,000 ppm in 2.75 h, and 1,000 ppm in 7.20 h in rats (Spencer et al., 1951). In one study with rabbits, the LD$_{50}$ for skin penetration was determined to be 3.89 (3.40-54.46) ml/kg. The toxic effects of single acute exposures to 1,2-dichloroethane were central nervous system depression, lung irritation, and injury to the liver, kidneys, and adrenals (Gohlke and Schmidt, 1972).

Chronic effects. When animals were exposed to 1,2-dichloroethane vapor for 7 h/day, 5/days/week, for 6 months, the maximal concentrations that produced no adverse effect were 400 ppm in rabbits, 200 ppm in rats, and 100 ppm in monkeys and guinea pigs (Heppel et al., 1946; Yllner, 1971). Significant chronic changes at higher concentrations included hepatic and renal damage. In other chronic studies, 500 ppm was not tolerated by rats, guinea pigs, or rabbits, and significant mortality occurred in the first 2 weeks; more than 90% of the animals were dead by the end of the fourth week. All the animals tolerated 100 ppm for a 17-week period (Yllner et al., 1971; Hofman et al., 1971).

Mutagenicity. Brem et al., (1974) have reported a mutagenic effect of 1,2-dichloroethane in *S. typhimurium* and DNA polymerase-deficient *E. coli*. It was the weakest, however, of the series of haloalkanes tested.

Carcinogenicity. No available data.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

1,2-Dichloroethane has been shown to be weakly mutagenic in two different mutagenicity screening tests. There is no data available on its potential carcinogenicity.

In view of the relative paucity of data on teratogenicity, carcinogenicity, and long term oral toxicity of 1,2-dichloroethane, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before final limits in drinking water can be established.

2,4-DICHLOROPHENOL

I. INTRODUCTION

2,4-Dichlorophenol is used mainly in organic synthesis. In the aquatic environment 2,4-D (2,4-dichlorophenoxyacetic acid) is decomposed to 2,4-dichlorophenol by sunlight and then to simpler compounds. 2,4-Dichlorophenol is slightly soluble in water (CRC Handbook of Chemistry and Physics, 1970-1971) and the highest concentration detected in United States drinking water was 36 µg/liter (EPA, 1975a).

II. METABOLISM

2,4-Dichlorophenol is excreted as a conjugate of glucuronic acid. Up to 16% may be excreted as sulfate in the urine of rabbits.

III. HEALTH ASPECTS

A. Observations in Man

No studies have been conducted to determine the effects of 2,4-dichlorophenol in man.

B. Observations In Other Species

Acute effects. The effects of an acute oral dose of 2,4-dichlorophenol have been examined in a variety of experimental animals; the oral LD_{50} is 1.63 g/kg in mice and 4.5 g/kg in male rats (Kobayashi *et al.*, 1972). On acute, subcutaneous administration, the LD_{50} was 1.73 g/kg in rats (Deichman, 1943). The intraperitoneal LD_{50} was 420 mg/kg in rats (Farquharson, *et al.*, 1958).

Chronic effects. In a study of the chronic effects of 2,4-dichlorophenol, it was found that the maximum dose producing no-observed-adverse-effect mice was 100 mg/kg/day (Kobayashi *et al.*, 1972). Kongiel-Chablo (1968) found that the administration of 0.2 - 2,000 mg/liter in the drinking water produced no effects, either on cholinesterase or on serum glutamic oxaloacetic transaminase in rats.

Mutagenicity. No available data.

Carcinogenicity. Boutwell and Bosch (1959) found that the topical application of 0.3% dimethylbenzanthracene in benzene as an initiator and 20% (312 mg/kg) 2,4-dichlorophenol for 19 weeks promoted papillomas and carcinomas in mice.

__Teratogenicity__. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

There is one report suggesting that topical 1,2-dichlorophenol may act as a co-carcinogen in promoting papillomas and carcinomas in mouse skin.

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity, and long term oral toxicity of 2,4-dichlorophenol, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

DI(2-ETHYLHEXYL)PHTHALATE

I. INTRODUCTION

Di(2-ethylhexyl)phthalate (DEHP) is commercially produced by the reaction of 2-ethylhexyl alcohol and phthalic anhydride. It is used in the manufacture of plasticizer, plastics, and organic pump fluid (EPA, 1975d). The United States production of di(2-ethylhexyl)phthalate in 1973 was over 370 million pounds (USITC, 1975).

Di(2-ethylhexyl)phthalate is insoluble (CRC Handbook of Chemistry and Physics, 1970-1971) and biologically persistent in water (EPA, 1975d). Four of the 10 finished-waters analysed by EPA contained this compound; the highest concentration was 30 μg/liter in Miami (EPA, 1975a). The Region V survey indicated that di(2-ethylhexyl)phthalate was present in 20 of 53 finished-water supplies; the highest concentration was 17 μg/liter, in Cincinnati (EPA, 1975b).

II. METABOLISM

Shaffer et al. (1945) studied the metabolism of di(2-ethylhexyl)phthalate in rats, rabbits, dogs, and man, and it was shown to be hydrolysed in all four. Oral doses were not completely absorbed. Dogs excreted 4 - 5% of an oral 2 g/kg dose as phthalate in 3 days, but rabbits excreted 26 - 65% phthalate in the same period. In man, 4 - 5% of a 10 g dose has been shown to be excreted as phthalate in the urine.

Williams and Blanchfield (1974) gave [^{14}C]DEHP as a single oral dose or in the diet to rats and found only limited retention and accumulation. Virtually all was excreted in urine or feces within 48 h. If the concentration was over 0.2% of the diet, the metabolic products were found in the feces. If only 10 ppm was fed, all excreted metabolic products were in the urine. Intravenous injected [^{14}C]DEHP in rats at 0.1 mg/kg was almost totally excreted as water-soluble metabolites in 24 h, according to Schulz and Rubin (1973).

II. HEALTH ASPECTS

A. Observations in Man

A dose of 10 g of DEHP in humans caused mild gastric disturbance and catharsis (Shaffer et al., 1945).

B. Observations In Other Species

Acute effects. The single-dose oral LD_{50} is variously reported to be from 26 - 34 g/kg in rats (Hodge, 1943; Shaffer *et al.*, 1945; Fassett, 1963; and Nikonorow *et al.*, 1973). Others have reported similarly high LD_{50}'s by other routes of administration and in other species (Calley *et al.*, 1966; Lawrence *et al.*, 1975).

Chronic effects. Nikonorow *et al.* (1973) fed DEHP at 0.35% to rats for 12 months and produced 30% mortality. Harris *et al.* (1956) fed various concentrations in the diet of rats and reported that those fed 0.5% for 2 years had lower weight gain, and enlarged livers and kidneys, but no micropathology. The 0.1% group was found to be comparable with the controls after 2 years.

When DEHP was given to rats at 2,000 mg/kg/day for 21 days, partial hydrolysis to the monoester was associated with the development of hepatomegaly, dilation of the endoplasmic reticulum and mitochondria, and changes in the activity of several enzymes (Lake *et al.*, 1975). Carpenter *et al.* (1953) fed DEHP to rats for 2 years and suggested that the no-adverse-effect dosage was 0.06 - 0.20 g/kg/day. In both guinea pigs and dogs fed for 1 year, the same authors found the no-adverse-effect dosage to be 0.06 g/kg/day.

Mutagenicity. No available data.

Carcinogenicity. In subacute and chronic feeding studies with rats, guinea pigs, and dogs by Carpenter *et al.* (1953), Harris *et al.* (1956), and Nikonorow *et al.* (1973) there were no increased instances of tumor formation, compared with controls, in any of the test species.

Teratogenicity. Nikonorow *et al.* (1973) studied the effect of DEHP (given before and during gestation) on reproduction in rats and found slightly lower fetal weights at 0.34 and 1.7 g/kg/day and slightly reduced placental weight at 1.7 g/kg/day. Peters and Cook (1973) found adverse effects on implantation under some conditions. Singh *et al.* (1972) studied the teratogenic potential of DEHP by intraperitoneal injections in rats on various days of gestation and found some gross fetal abnormalities and resorptions at 10 ml/kg. The chick embryo test reported by Bower *et al.* (1970) produced no abnormalities. Prehatching death was more common in controls than in test samples.

Massive single doses of DEHP (12.78, 19.17, and 25.56 ml/kg) in male mice produced changes in the percent of females impregnated, implants per pregnancy, fetal deaths per pregnancy, and litter size per pregnancy in inseminated females. Half the members of the 25.56 ml/kg group died (Singh *et al.*, 1974).

V. CONCLUSIONS AND RECOMMENDATIONS

The available data on di(2-ethylhexyl)phthalate do not suggest that it might be a health hazard at the concentrations at which it has been found.

An ADI was calculated on the basis of the chronic toxicity data. Based on this data the ADI is 0.6 µg/kg/day. The calculations and available chronic toxicity data are summarized in Table VI-51.

TABLE VI-51. Summary of Chronic Toxicity Data for di(2-ethyl hexyl)phthalate

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse-effect Level or Lowest Minimal-effect Level	Effect Measured	Reference
Rat	2 yrs.	0-0.2 g/kg/day, 64 animals per group	0.06 g/kg/day[c] (oral)	No adverse effect	Carpenter et al., 1953
Guinea pig	1 yr.	0-0.64 g/kg/day, 46 animals per group	0.019 g/kg/day (oral)	No adverse effect	Carpenter et al., 1953
Rat	2 yrs.	0-0.4 g/kg/day 86 animals per group	0.04-0.08 g/kg/day (oral)	No adverse effect	Harris et al., 1956

Using an uncertainty factor of 100, the suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{60}{100} = 0.6 \text{ mg/kg/day (ADI)}, \ 0.6 \times 70^{a} \times 0.1^{b} = 4.2 \text{ mg/liter.}$$

---

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate no-adverse-effect level.

2,4-DIMETHYLPHENOL

I. INTRODUCTION

2,4-Dimethylphenol is one of the five isomers of xylenol (dimethylphenol). It is the cresylic acid or tar acid fraction of coal tar. It is used principally in the manufacture of phenolic antioxidants, pharmaceuticals, plastics, resins, solvents, disinfectants, insecticides, fungicides, rubber chemicals, wetting agents, and dyestuff (EPA, 1975d). It is slightly soluble in water and has been found in finished water (EPA, 1976).

II. METABOLISM

The metabolism of 2,4-dimethylphenol in animals is very similar to that of the cresols. In rabbits the average percentages of metabolites isolated included: 2% as free nonacidic phenol; 13% as ethereal sulfate; 46% as ether glucuronide; and 64% as ether-soluble acid (Bray *et al*., 1950).

III. HEALTH ASPECTS

A. Observations In Man

The adverse health effects of 2,4-dimethylphenol in man have not been examined.

B. Observation In other Species

Acute effects. The effects of acute oral administration of 2,4-dimethylphenol have been examined in mice, rats, and rabbits. The oral LD_{50}'s are 809 mg/kg in mice (Ushdovini *et al*., 1974) and 3,200 mg/kg in rats (Registry of Toxic Effects of Chem. Substances, 1975; Ushdovini *et al*., 1974). No appreciable toxic effect has been seen at 273-425 mg/kg in rabbits (Ushdovini *et al*., 1974). Topical administration has been shown to be lethal to mice at 5,600 mg/kg; the topical LD_{50} in mice is 1,040 mg/kg (Registry of Toxic Effects of Chem. Substances, 1975; Ushdovini *et al*., 1974). The intraperitoneal LD_{50} is 150 mg/kg in mice.

Chronic effects. No available data.

Mutagenicity. No available data.

Carcinogenicity. In a study of the chronic effects of 2,4-dimethylphenol in mice, Boutwell and Bosch (1959) showed that topical application after the administration of 1% dimethylbenzanthracene (as an initiator) produced papillomas in 50% and carcinomas in 11% at 15 weeks; by 23 weeks, 18% developed carcinomas. When dimethylbenzanthracene was used as the initiator and 20% 2,4-dimethylphenol in benzene as the promoter, 24 weeks of intermittent topical application produced papillomas in 63% and carcinomas in 5% by 39 weeks, 42% developed carcinomas. When 10% 2,4-dimethylphenol was applied topically for 20 weeks in the absence of an initiator, 31% had papillomas, and no carcinomas were observed. By 24 weeks, 12% had carcinomas.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

2,4-Dimethylphenol appears to be a topical cocarcinogen, but its role as a primary cancer-producing agent is uncertain. Its potential role in cancer production warrants consideration of further testing. An in vitro mutagenicity assay should be carried out to further evaluate its mutagenic potential.

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity and long term oral toxicity of 2,4-dimethylphenol, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

DIPHENYLHYDRAZINE

I. INTRODUCTION

Diphenylhydrazine is an intermediate in the production of benzidine. It is slightly soluble in water and the highest concentration detected in United States drinking water was 1 μg/liter (EPA, 1975a).

II. METABOLISM

No data are available on the metabolism of diphenylhydrazine in man or animals.

III. HEALTH ASPECTS

A. Observations In Man

The adverse health effects of diphenylhydrazine in man have not been examined.

B. Observations In Other Species

Acute effects. The oral LD_{50} of diphenylhydrazine is 301 mg/kg in rats (Mason Research Institute Report, 1971).

Chronic effects. No available data.

Mutagenicity. No available data.

Carcinogenicity. In a study to examine the carcinogenic effects of this compound, 60 mg/kg administered subcutaneously produced a wide variety of benign and malignant tumors in Sherman rats (Spitz et al., 1950). In a similar study, subcutaneous injection of 40 - 60 mg/kg/week or ingestion of 30 mg/kg/day for up to 500 days induced uterine, mammary, and liver tumors in rats (Pliss, 1974). An oral dose of 2 mg/day for the entire life span of Wistar rats produced no increase in the incidence of tumors (Marhold et al., 1968). A subcutaneous dose of 5 mg/kg/week or 2 mg/kg/day for up to 500 days resulted in subcutaneous sarcomas and hepatomas in mice (Pliss, 1974).

Teratogenicity. No available data.

IV CONCLUSIONS AND RECOMMENDATIONS

Diphenylhydrazine is a suspected carcinogen in humans because of its structural relationship to benzidine, which is an established human bladder carcinogen. Recent studies in rats and mice have shown that diphenylhydrazine produces both bnign and malignant tumors when administered subcutaneously. The results of oral ingestion studies are equivocal and are not adequate to establish a cancer risk estimate.

In view of the relative paucity of data on the mutagenicity, teratogenicity and long term oral toxicity of diphenylhydrazine, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

The available chronic toxicity data are summarized in Table VI-52.

TABLE VI-32. Summary of Chronic Toxicity Data for Diphenylhydrazine

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse-effect Level or Lowest Minimal-effect Level	Effect Measured	Reference
Rat	500 days		60 mg/kg/wk Subcutaneously, 30 mg/kg/day Or 11y	Urinary, mammary and liver tumors	Pliss, 1974
Rat	Life time		2 mg/day (oral)	No increase in the incidence of tumors	Marhold et 1968
Mouse	500 days		8 mg/kg/day (subcutaneous) 5 mg/kg/week (subcutaneous)	Subcutaneous sarcomas and hepatomas	Pliss, 1974

[This compound is an animal carcinogen]

HEXACHLOROETHANE

I. INTRODUCTION

Hexachloroethane (HCE) is used in organic synthesis, as a retarding agent in fermentation, as a substitute for camphor in nitrocellulose, in pyrotechnics and smoke devices, and in the manufacture of explosives, solvents, and medicines. It can be formed in small quantities by chlorination (EPA, 1975). It is insoluble in water and very persistent. Of the 10 water supplies surveyed by the EPA (1975a), only Miami's finished water contained hexachloroethane, at 0.5 μg/liter.

II. METABOLISM

Hexachloroethane was detected as a metabolite of carbontetrachloride in rabbits following a 1 ml/kg dose in olive oil. Fat contained the highest concentration of HCE, muscle the lowest; tissue concentrations reached a peak at 24 h, but persisted for as long as 48 h (Fowler 1969).

III. HEALTH ASPECTS

A. Observations In Man

No studies have been conducted to examine the acute, subchronic, or chronic effects of hexachloroethane in man.

B. Observations In Other Species

Acute effects. The Toxic Substances List (1974) notes that the lowest reported acutely lethal dosages of HCE are 325 mg/kg administered intravenously in dogs and 4,000 mg/kg administered subcutaneously in rabbits.

In a study of the subacute effects of hexachlorethane by Tugarinova et al. (1963), 12 mice received 310 mg/kg orally once a day for 10 days. Macroscopic examination of the animals revealed no cumulative effects.

Chronic effects. Chronic experiments with 19 male rats (weighing 200 - 240 g) and 12 female and eight male rabbits weighing (2,100 - 2,800 g) given hexachloroethane orally at 0.05 mg/kg/day for 5.5 months showed no signs of toxicity measured by body weight, motor reflexes, and blood chemistry. Histopathologic evaluation of brain, heart, liver, kidneys, spleen, stomach, and intestine were negative (Tugarinova et al., 1963).

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. No available data.

V. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity, and long term oral toxicity of hexachloroethane, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

HEXACHLOROPHENE

I. INTRODUCTION

Hexachlorophene (HCP), or 2,2'-methylene-bis(3,4,6-trichlorophenol), has been used as an antibacterial agent in a wide variety of consumer products, including soaps and deodorants (Gump, 1969; Kimbrough, 1976.) It has also been used as an antifungal agent to treat various citrus fruits and vegetables.

HCP has been identified in surface water (Buhler et al., 1973; Sims and Pfaender, 1975) at concentrations as high as 48 ppb. HCP in drinking water at 0.01 ppb has also been reported (Buhler et al., 1973; EPA, 1975). HCP is practically insoluble in water (CRC Handbook of Chemistry and Physics, 1970-1971).

II. METABOLISM

Studies in rabbits, rats, and cows (Wit and Van Genderen, 1962) with [^{14}C]HCP showed that it is absorbed orally, that most of what is absorbed is excreted via the feces within 5 - 7 days, and that in rabbits the half-life is 17.8 h. Gandolfi and Buhler (1974) demonstrated after intraperitoneal injection in rats that the major metabolite is a monoglucuronide and that there is extensive enterohepatic circulation. Absorption through the skin has resulted in mean blood concentrations of 0.2 µg/ml in adult humans (Feldman and Maibach, 1970; Butcher et al., 1973) and 0.049 µg/ml in human infants (Plueckhahn, 1973).

II. HEALTH ASPECTS

A. Observations In Man

Wear et al. (1962) reported that an oral dose of 2 - 10 g (33-166 mg/kg) may be fatal in adults. Lustig (1963) cited the case of a (16-kg) child that died after ingesting 200-300 mg (16 mg/kg), and Martinez et al. (1974) described the case of a 17-year-old boy who ingested 1,350 mg and died 61 h later. In another case, an infant was accidentally given 17 mg/kg/day orally for 7 days; the child developed gastrointestinal irritation, dehydration, neuromuscular effects, and shock, but recovered completely (Pilapil, 1966). Shuman et al. (1974) reported that human neonates weighing less than 1,400 g at birth are very susceptible to central nervous system effects of the compound.

There are many reports in the literature concerning intoxication by HCP following accidental or suicidal ingestion or exposure to preparations containing this antibacterial agent (Kimbrough, 1976).

Children poisoned with HCP develop myelin edema; i.e., status spongiosus (Mullick, 1973; Shuman *et al.*, 1974). While humans undergoing treatment for *Clonorchis sinensis* tolerated a single 20 mg/kg oral dose of HCP, three successive 20 mg/kg/day doses of the antibacterial produced intoxication in treated patients (Chung *et al.*, 1963; Liu *et al.*, 1963).

B. Observations in Other Species

Acute effects. In acute studies, the oral LD_{50} in mice was reported to be 187 mg/kg (Gump, 1969), 80 mg/kg (Florestano, 1949), and 67 mg/kg (Chung *et al.*, 1963). Oral LD_{50} values for male and female Wistar rats were 58 - 87 and 63 - 87 mg/kg, respectively, (Nakaue *et al.*, 1973) while for Sherman strain rats they were 66 and 56 mg/kg, respectively (Gaines *et al.*, 1973). Juvenile rats are more resistant to HCP than adults and oral LD_{50}s for 10-day, 32-day and adult rats were 9, 111, and 55 mg/kg, respectively (Nieminen *et al.*, 1973). Acute toxicity appears to be a function of age and extent of myelination of the central nervous system.

Dog pups given 15 mg/kg oral dose of HCP exhibited neurotoxicity and died whereas an oral dose of 7.5 mg/kg HCP only produced excitability (Edds and Simpson, 1974). The oral LD_{50} for young dogs was estimated at 15 - 30 mg/kg.

The loss of pupillary response and blindness was found in sheep after receiving a single 20 - 80 mg/kg oral dose of HCP (Udall and Malone, 1970). Weanling rats given a single 100 mg/kg oral dose of HCP developed weakness of the hind legs and showed severe vacuolization in the myelinated areas of the brain (Kimbrough, 1973). Severe testicular degeneration and detectable liver changes, including increased mitotic activity were found in rats given 75 mg/kg HCP (Thorpe, 1967).

Subchronic and chronic effects. In a study of the subchronic effects of HCP, rats fed 0.02 and 0.04% HCP in the diet for 30 days showed mild toxicity with reduced growth at the lowest dose. At the higher dose, liver and kidney pathology developed (Gump, 1969). Rats fed 20, 65, and 200 ppm HCP for 90 days showed no evidence of toxicity (Vaterlaus and Hostynek, 1972). A simillar study was recently reported by Kennedy *et al.* (1976) in which male and female Charles River CD strain rats were fed dietary levels of 0, 20, 65, or 200 ppm commercial grade HCP (G-11) or received 2.5 mg/kg daily oral doses of HCP over a 90 day period. A moderate degree of vacuolization in the cerebellum was observed in 2 of 20 rats at the 200 ppm HCP level (20 mg/kg/day) but no signs of CNS disorders or other abnormalities were observed in the treated animals. In a second study with the same strain of rats (Kennedy *et al.*, 1976), daily 0, 20, and 40 mg/kg oral doses of HCP were administered for 6 weeks. Growth was depressed at 40 mg/kg/day HCP. Vacuolization of the brain was seen in animals given 40 mg/kg/day and, to a lesser extent, in those receiving 20 mg/kg/day. The histopathologic changes of the brain elicited by HCP were barely detectable after a recovery period of 84 days and hence are reversible.

In contrast to these results, considerably greater toxicity was found with HCP in other rat studies. Some Sherman rats fed 500 ppm HCP for a period of 90 days died after developing severe hind limb paralysis with accompanying brain edema (Gaines *et al.*, 1973; Kimbrough and Gaines, 1971).

In a chronic study, no paralysis was seen in rats fed 20 and 100 ppm HCP for 250 days but appreciable vacuolization of the brain occurred at the higher dose (Gaines *et al.*, 1973). With Wistar strain weanling rats fed for 112 days, 400 ppm (28.9 mg/kg/day) HCP produced paralysis and death (Nakaue *et al.*, 1973). Rats fed 200 ppm (14.9 mg/kg/day) developed an initial paralysis but recovered after about two weeks, while rats fed 100 ppm (7.7 mg/kg/day) appeared normal. Brain edema was seen, however, with decreasing severity in the groups fed 400, 200, and 100 ppm HCP. No adverse effects were observed at 50 ppm (3.7 mg/kg/day).

Mutagenicity. The possible mutagenic effects of HCP were evaluated by a dominant lethal study in mice and a host-mediated assay in rats with *Salmonella Typhimurium* (Arnold *et al.*, 1975). No evidence for mutagenicity was seen in mice given single doses of 2.5 or 5 mg/kg HCP (dominant lethal) or in rats fed 100 or 200 ppm HCP over a 90 day period (host-mediated).

Carcinogenicity. Twice weekly application of 1, 5, and 10 mg HCP on the skin of Swiss mice over their lifetime caused local and systematic toxicity but no evidence of carcinogenicity was seen (Stenback, 1975).

Teratogenicity. Kimmel *et al.* (1974) examined the teratogenic effects of vaginally administered HCP. Doses of 80 mg/kg (equivalent to about 1,000 ppm in the diet) and above were teratogenic in Charles River rats while a 20 mg/kg dose was without adverse effect. The defects produced at the highest dose (300 mg/kg) included hydrocephaly, microthalmia, wavy ribs, and urogenital defects. CD strain rats received oral doses of 1, 15, or 30 mg/kg/day HCP on days 6 - 15 of gestation while NZW rabbits were given 1, 3 or 6 mg/kg/day HCP on days 6 - 18 of gestation (Kennedy *et al.*, 1975b). Rat fetuses exposed to 30 mg/kg/day HCP had a low frequency of eye and skeletal defects (10/209 angulated ribs) while skeletal changes (3/175 had rib malformations) appeared in rabbit fetuses exposed to 6 mg/kg/day HCP. There was no increase in prenatal death at any dosage level.

Administration of HCP to three successive generations of albino rats at dietary levels of 12.5, 25, and 50 ppm failed to produce any changes with respect to mating, fertility, length of gestation, and number of deliveries (Kennedy *et al.*, 1975a). There was no detectable adverse effect on the mothers or on the progeny.

IV. CONCLUSIONS AND RECOMMENDATIONS

The principal toxicologic and pathologic effect of hexachlorophene is on the central nervous system, where reversible edematous vacuolation of the myelin sheaths of the white matter occurs if the plasma content is maintained over a long period at 1.2 μg/ml or greater. Newborn humans and laboratory animals are more susceptible to this effect than adults.

An ADI was calculated on the basis of the available chronic toxicity data. Based on this data the ADI is 0.0012 mg/kg/day.

The calculations and available chronic-toxicity data on animals are summarized in Table VI-53.

Hexachlorophene does not appear to be an active carcinogen or teratogen, although long-term chronic-toxicity studies integrating carcinogenicity and target organ toxicity are recommended, to assemble more data. Since there are no reported two year chronic toxicity studies with HCP, it is suggested that such studies be undertaken before a final assessment of the long term hazards of HCP exposure can be made.

TABLE VI-51. Summary of Chronic Toxicity Data for Hexachlorophene

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse effect Level or Lowest Minimal-effect Level	Effect Measured	Reference
Rat	14 wks.	0-25 mg/kg/day, 10-12 animals per group	≤5 mg/kg/day (oral)	Toxicity and Pathology	Kimbrough & Gaines, 197
Rat	37 wks.	0-100 ppm in diet, 20 animals per group	20 ppm (1.16 mg/kg/day)[c]	No toxic effect	Gaines et al. 1973
Rat	16 wks.	0-400 ppm in diet, 8 animals per group	50 ppm (1.7 mg/kg/day)	No toxic effect	Nakaue et al. 1973

Using an uncertainty factor of 1,000, the suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{1.16}{1,000} = 0.00116 \text{ mg/kg/day (ADI)}, \; 0.00116 \times 70^{a} \times 0.1^{b} = 0.008 \text{ mg/liter.}$$

Mean daily dosages indicated by authors.

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse-effect level.

O-METHOXYPHENOL

I. INTRODUCTION

O-Methoxyphenol (guaiacol) is produced in wood processing or by chemical synthesis. It is used in the manufacture of medicines, guaiacol compounds, and perfumes (Chem. Dict. 1972). The solubility of o-methoxyphenol is 1 g in 50 - 70 ml of water (Merck Index, 1968). It has been detected in finished water in the lower Mississippi River area (EPA, 1972).

II. METABOLISM

Methoxyphenol is largely absorbed from the digestive tract and stored in the blood, kidneys, and respiratory organs (Jurgens, 1920). It is excreted in rabbits in combined form with sulfate (15%) and glucuronic acid (72%) (Stefano and Quirico, 1939).

III. HEALTH ASPECTS

A. Observations In Man

There have been no investigations of the adverse health effects of o-methoxyphenol in man.

B. Observations In Other Species

Acute effects. The LD$_{50}$ was shown to be 3.74 mg/kg in rabbits (Stefano and Quirico, 1939). The minimal lethal injected dose in rats was shown to be 50 mg/kg by Tedeschi and DeCicco (1958). They found that, when o-methoxyphenol was injected into pregnant rats, it was fatal to the fetus; when similar doses were injected into male animals, serious disorders of the testes and destruction of the germinal epithelium were observed. The oral LD$_{50}$ in rats has been shown to be 725 mg/kg by Taylor *et al.* (1964).

The lethal oral dose of o-methoxyphenol in mice is 0.4 g/kg (Ono, 1920). Ono also found that a 0.15% solution caused paralysis of the heart muscle, and a 0.6% solution, paralysis of intestinal smooth muscle.

In toxicologic studies with o-methoxyphenol, it was found that the compound exerted a hemolytic action on cattle blood (Stefano and Quirico, 1939) and interfered with RNA synthesis, protein synthesis, and, to a small degree, mitochondrial respiration in rats (Taylor *et al.*, 1964). Vanderhoek and Lands (1973) reported the inhibition of fatty acid oxygenase in sheep vesicular gland tissue on exposure to o-methoxyphenol and [illegible]

(1919) found that the compound induced leukopenia that led to leukocytosis in rodents.

Chronic effects. No available data.

Mutagenicity. No avialable data.

Carcinogenicity. Methoxyphenol has been found to contribute to the carcinogenic effect of tobacco smoke in rats (Wynder and Hoffamn, 1963).

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity, and long term oral toxicity of O-methoxyphenol, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

METHYL CHLORIDE

I. INTRODUCTION

Methyl chloride (chloromethane) is produced commercially by the chlorination of methane or the action of hydrochloric acid on methanol. It is used in the manufacture of silicones, synthetic rubber, tetraethyl lead, methyl cellulose, refrigerants, organic chemicals, and fumigants; as a low-temperature solvent, as a catalyst carrier in polymerization; as a methylating agent; as a propellant; and as an herbicide (EPA, 1975d). The United States production of methyl chloride in 1973 was 544 million pounds (USITC, 1975).

Methyl chloride is slightly soluble in water (CRC Handbook of Chemistry & Physics, 1970-1971). Five of the 10 water supplies surveyed by the EPA (1975a) contained methyl chloride.

II. METABOLISM

In human breath-analysis studies of some aliphatic halogenated hydrocarbons, Morgan et al. (1972) demonstrated that methyl chloride did not have the rate of excretion that would be predicted on the basis of its partition coefficient compared with the other similar compounds studied. It was later postulated that this anomalous behavior of methyl chloride may be due to an enzyme-catalysed methylation of red-cell sulfhydryl groups. This is in agreement with the findings of Redford-Ellis and Gowenlock (1971a), who showed that [^{14}C]S-methylglutathione (GSMe) and [^{14}C]S-methylcysteine (S-Me Cys) were formed from the interaction of radioactively labeled methyl chloride with human blood and liver, brain, and kidney homogenates.

III. HEALTH ASPECTS

A. Observations In Man

No documented information on the adverse health effects of methyl chloride in man is available.

B. Observations In Other Species

Acute effects. The effects of a single inhalation exposure to methyl chloride were examined as functions of time and dose in a variety of experimental animals. A concentration of 150,000 - 300,000 ppm proved lethal to most animals in a short period; 20,000 - 40,000 ppm proved dangerous in 30 - 60 m; 7,000 ppm produced no serious effects in up to 60 m of exposure; and 500 - 1,000 was ineffective for up to 8 h (Patty Vol. II, 1963).

Chronic effects. Smith and von Oettingen (1947a,b) exposed guinea pigs, mice, dogs, rabbits, and rats to methyl chloride at 1,000 ppm for 6 h/day, 6 days/week, for up to 175 days. This concentration was judged toxic, on the basis of central nervous system (neuromuscular effects) and decreased survival. At 500 ppm, rats showed no effects; but the other animals, including two monkeys, showed some response. Effects were usually delayed with these lower concentrations and remained for months after exposure. Common signs among most species were loss of leg movement, muscle contractions, tremors, and hyperactive tendon reflexes. Three of 4 dogs died after four weeks or less of exposure, and the two monkeys died after 17 weeks of exposure. At 300 ppm, no effects were observed in any of the animals.

Evtushenko (1966) indicated that rats exposed to methyl chloride at 120 and 20 ppm showed formaldehyde in the blood and developed anemia and reticulocytosis. There were some undescribed pathologic central nervous system changes and some eye effects. On the basis of the above work a U.S.S.R. value for the TLV was suggested at 2.5 ppm.

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity, and long term oral toxicity of methyl chloride, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before final limits in drinking water can be established.

METHYLENE CHLORIDE

I. INTRODUCTION

Methylene chloride (dichloromethane) is used in the manufacture of paint and varnish removers, insecticides and fumigants, solvents, cleaners, pressurized spray products, fire extinguishers, and Christmas tree bubble lights (Chemistry Dictionary, 1972). It is produced by chlorination of methane or methyl chloride. The United States production in 1973 was over a half-billion pounds (USITC, 1975).

Methylene chloride is soluble at about 1 part to 50 parts of water (Merck Index, 1968). It is formed during chlorination water treatment. The Region V survey showed that 8% of the finished-water supplies contained methylene chloride, but only 1% of the raw-water supplies. The mean concentration in finished water was <1 μg/liter (EPA, 1975b). Nine of the 10 water supplies surveyed by the EPA (1975a) contained methylene chloride; Lawrence, Massachusetts had the highest concentration, 1.6 μg/liter.

II. METABOLISM

DiVincenzo and Hamilton (1975) administered [^{14}C]methylene chloride to Sprague Dawley rats at 412-930 mg/kg. Methylene chloride was largely eliminated unchanged in the expired air during the first 2 h. After 24 h, only 2% of the original dose remained in the body. This 2% was found mostly in the liver, kidneys, and adrenal glands.

It has been shown by DiVincenzo and Hamilton (1975) and Soucek (1961) that some methylene chloride is converted in the body to carbon monoxide; this results in an increase in carboxyhemoglobin concentration. Blood carbon monoxide content is not directly related to the exposure concentration of methylene chloride. A review of the literature shows that there is a wide variation in carboxyhemoglobin concentration in persons exposed to a given concentration of methylene chloride for a given period and a lack of consistent correlation in measurement or calculation of carboxyhemoglobin. Furthermore, the significance of increased blood carboxyhemoglobin has not been satisfactorily determined.

III. HEALTH ASPECTS

A. Observations In Man

Raleigh (1974) reported an inhouse study on 562 employees; 103 were reportedly in the highest-exposure group, being exposed to methylene chloride at 50-100 ppm. There was no increase in the incidence of cardiovascular, gastrointestinal (including liver), genitourinary, or central nervous system disease in the exposed groups, compared with a nonexposed worker population.

The NIOSH (1976) recommended that occupational exposure to methylene chloride not exceed 75 ppm determined as a time-weighted average exposure for up to a 10-h workday.

B. Observations In Other Species

Acute effects. The acute oral LD_{50} values are 1.6 - 2.3 ml/kg for rats (Kimura, *et al.*, 1971). The intraperitoneal LD_{50} values are 1.50 ml/kg for mice and 0.95 ml/kg for dogs (Klaassen and Plaa, 1967).

Chronic effects. In a chronic study, Bornmann and Loeser (1967) reported no adverse effects in rats maintained on drinking water containing methylene chloride at 2.25 g/18 liters for 91 days. In a study on the effects of methylene chloride inhalation, Heppel *et al.* (1944) showed no adverse effects on dogs and rabbits in a 6-month exposure to 5,000 ppm; a slight weight reduction was observed, however, in guinea pigs. Some liver injury was found after 7.5 weeks at 10,000 ppm.

Mutagenicity. Methylene chloride was negative in a *Drosophila* mutagenicity test (Filippova *et al.*, 1967)

Carcinogenicity. No available data.

Teratogenicity. Methylene chloride vapor was not teratogenic in rats and mice at 1,250 ppm (Schwetz *et al.*, 1975). Both species were exposed for 7 hours daily on days 6 through 15 of gestation. No fetal toxicity or teratogenicity was found.

IV. CONCLUSIONS AND RECOMMENDATIONS

Methylene chloride was not teratogenic when inhaled in one species of rats and mice. In view of the relative paucity of data on the mutagenicity, carcinogenicity, and long term oral toxicity of methylene chloride, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before final limits in drinking water can be established.

METHYL METHACRYLATE

I INTRODUCTION

Methyl methacrylate is the monomer for polymethacrylate resins and used in impregnation of concrete. The United States production of it in 1973 was over 706 million pounds (USITC, 1975). This compound is slightly soluble in water (CRC Handbook of Chemistry & Physics, 1970-1971). The highest concentration of methymethacrylate detected in United States drinking water was less than 1 μg/liter (EPA, 1975a).

II. METABOLISM

Methyl methacrylate is metabolized in rat liver slices via the citric acid cycle. It undergoes hydroxylation to a primary alcohol followed by oxidation to an aldehyde; finally the compound is deformylated to pyruvic acid (Pantucek, 1969).

III. HEALTH ASPECTS

A. Observations In Man

In a study by Nilkov *et al.* (1966), small amounts of methyl methacrylate vapor found in casting plants was found to induce functional abnormalities in the nervous system of plant workers. In another series of experiments, exposure to methacrylate glue in the placement of bone protheses was also found to induce severe hypotension and some cases cause death. The studies did not determine, however, whether the adverse reactions were the result of the methacrylate or bone marrow embolism (Newens and Voltz, 1972; Cooper, 1975; Breed, 1974).

B. Observations In Other Species

Acute effects. In acute studies, the oral LD_{50} of methyl methacrylate has been determined for a variety of experimental animals; guinea pig, 6.3 ml/kg; rat, 8.4 - 10 ml/kg; and dog, 5.0 ml/kg (Spealman *et al.*, 1945; Deichman, 1941). The intraperitoneal LD_{50} values have also been calculated; rats 1.8 ml/kg; mouse 10 ml/kg; and guinea pig, 2.0 ml/kg. The LD_{50} values for the subcutaneous injection of methacrylate are: rat, 7.5 ml/kg; dog, 4.5 ml/kg; and guinea pig, 6.3 ml/kg (Spealman *et al.*, 1945).

Chronic effects. In chronic studies, rats and dogs were given drinking water containing 6, 60, and 2000 ppm and 10, 100 and 1000 ppm methyl methacrylate, respectively, for 2 years. No clinical, laboratory or pathological evidence of toxicity was observed in either group of animals (Borzelleca *et al.*, 1964).

Mutagenicity. No available data.

Carcinogenicity. In a study by Lavorgna *et al.* (1972), subcutaneous implants of freshly polymerized methyl methacrylate for up to 19 months increased the incidence of local fibrosarcoma compared to a glass implant control in rats. In another study, Laskin, *et al.* (1954) found that subcutaneous implants of polymerized methyl methacrylate induced local fibrosarcomas in mice.

Teratogenicity. Doses of 0.13 - 0.44 ml/kg methyl methacrylate injected into pregnant rats on days 5, 10, and 15 of gestation were found to affect resorptions, fetal survival and fetal size at all doses. Hemangiomas were also observed in some fetuses from the highest dose group. No skeletal abnormalities were observed at any dose (Singh *et al.*, 1972a).

III. RECOMMENDATIONS AND CONCLUSIONS

Chronic toxicity studies in rats and dogs indicate that ingested methyl methacrylate does not pose a serious threat to humans or animals. Teratogenicity studies indicate that it can affect fetal growth and survival in rats when injected during specific days of gestation. An ADI was calculated on the basis of the avialable chronic toxicity data. The ADI is 0.1 mg/kg/day. The calculations and available chronic toxicity data are summarized in Table VI-54.

TABLE VI-34. Summary of Chronic Toxicity Data for Methyl Methacrylate

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse effect Level or Lowest Minimal-effect Level	Effect Measured	Reference
Rat	2 yrs.	0,6,60,2000 ppm in drinking water, 25 animals per group	2,000 ppm (100 mg/kg/day)[a,d]	No adverse effect	Borzelleca et al., 1964
Dog	2 yrs.	0-1,000 ppm in drnkg. wtr. 2 animals per group	1,000 ppm	No adverse effect	Borzelleca et al., 1964

Using an uncertainty factor of 1,000, the suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{100}{1,000} = 0.1 \text{ mg/kg/day (ADI)},\ 0.1 \times 70^{b} \times 0.1^{c} = 0.7 \text{ mg/liter.}$$

[a] Assume weight of rat = 0.4 kg and daily food consumption of rat = 0.02 kg.

[b] Assume average weight of human adult = 70 kg.

[c] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[d] Best study from which to calculate suggested no-adverse-effect level.

NICOTINE

I. INTRODUCTION

Nicotine [1-methyl-2(3-pyridyl)pyrrolidine] is commercially produced by distilling tobacco. It is used in some drugs, and insecticides, and in tanning. Nicotine is very soluble in water (Chemistry Dictionary 1972). Of the 10 water utilities surveyed by the EPA (1975a), only the finished water of Miami contained nicotine at 3 μg/liter.

II. METABOLISM

In a study of the metabolism of nicotine in rats, 8 - 12% of the compound was found to be excreted unchanged; 40% was excreted in 3 h, with complete excretion in 16 h. The major metabolite of nicotine is cotinine (Bowman *et al.*, 1959). In mice, dogs, and guinea pigs, exposure to nicotine smoke permits its detection in visceral storage compartments, including liver, kidneys, lungs, and brain (Bennett *et al.*, 1954).

III. HEALTH ASPECTS

A. Observations In Man

The symptoms of nicotine intoxication are nausea, vomiting, diarrhea, confusion, twitching, and convulsions. A dose of 40 mg of nicotine taken orally is fatal in man. Nicotine has also been shown to induce blood-sugar changes in 24 h; 0.3 mg/kg was the lowest no-effect dose (Wilson and DeEds, 1936a).

B. Observations In Other Species

Acute effects. The acute oral LD_{50} for mice is 230 mg/kg (Barlow and McLeod, 1969) and 10 mg/kg for rats (Kenaga, 1966). The acute symptoms include respiratory toxicity and transitory hyperglycemia in rats. A change in blood sugar has been observed after 2 h with doses of nicotine greater than 0.5 mg/kg.

Chronic effects. Nicotine has been shown to decrease the growth of rats after 100 days with doses of 12.5 mg/kg and in 200 days with doses of 10 mg/kg (Wilson and De Eds, 1936b).

Mutagenicity. Nicotine was negative on a *Salmonella*/microsome mutagenicity assay (McCann *et al.*, 1975).

Carcinogenicity. Nicotine has been found to act as a cocarcinogen when applied to mouse skin with benzo(a)pyrene and 12-O-tetradecanoylphorbol-13-acetate (Chem. Eng. News, 1976). Oxidized nicotine applied to the skin of mice resulted in lung adenomas. In another strain of mouse (CBA), commercial nicotine produced no lung tumors.

Teratogenicity. Nicotine was teratogenic in mice when injected at 25 mg/kg on days 9-11 of gestation. Skeletal defects and occasional cleft palates were produced (Nishimura and Nakai, 1958). Nicotine was also teratogenic in swine at an oral dose of 1058 ppm (Menges et al., 1970).

IV. CONCLUSIONS AND RECOMENDATIONS

At high doses, nicotine is quite toxic and lethal. Nicotine is metabolized readily, principally to cotinine. Nicotine is teratogenic in mice only at high doses. Evidence on carcinogenicity is equivocal, but it is a cocarcinogen.

In view of the relative paucity of data on the carcinogenicity, and long term oral toxicity of nicotine, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

PENTACHLOROPHENOL

I. INTRODUCTION

Pentachlorophenol (PCP) has been used since 1936 for wood preservation (Spencer, 1973). Domestic production of PCP is estimated at 46 million pounds a year (National Academy of Sciences, 1975).

PCP is produced commercially by the chlorination of phenol (Spencer, 1973). Commercial-grade PCP contains 88.4% PCP, 4.4% tetrachlorophenol, 6.2% higher chlorinated phenoxyphenols, less than 0.1% trichlorophenol, and various dibenzo-p-dioxins and dibenzofurans (Johnson *et al.*, 1973; Schwetz *et al.*, 1974). The highly toxic tetrachlorodioxins are not found in technical PCP. PCP is soluble in water at 20 ppm at 30°C. It is not very volatile, as evidenced by a vapor pressure of 1.1×10^{-4} mm Hg at 20°C (Spencer, 1973). Concentrations of 0.70 and 0.06 ppb PCP have been observed in river and treated drinking water, respectively (Buhler *et al.*, 1973). The highest concentration of PCP reported in United States drinking water was 1.4 ppb (EPA, 1975e).

II METABOLISM

A pharmacokinetic profile of pentachlorophenol in monkeys and an elimination study with [^{14}C]pentachlorophenol and its metabolites in rats have been conducted (submitted for publication in Toxicol. Appl. Pharmacol.). These studies showed that 96% of a 10 mg/kg dose of PCP in rats is eliminated rapidly with a half life of from 13 - 17 h depending on sex. PCP is excreted either as tetrachlorohydroquinone (16%) or as a PCP glucuronide conjugate in the urine (9%) or a free PCP (75%). The excretion pattern in monkeys was slower than in rats and almost all PCP was excreted unchanged in urine. It was suggested that the monkey may be a better animal model and more closely approximate human pharmacokinetics.

III. HEALTH ASPECTS

A. Observations in Man

Menon (1958) reported loss of appetite, respiratory difficulties, anesthesia, hyperpyrexia, sweating, dyspnea, and rapidly progressive coma in humans exposed to PCP.

A number of cases of human poisoning by PCP are reviewed by Armstrong *et al.* (1969). The minimum lethal dose for humans is estimated to be 29 mg/kg (The Toxic Substances List, 1974). Work done in Russia has established a maximum permissible concentration of 40 ng/m^3 PCP in the air (Tabakova, 1969).

B. Observations In Other Species

Acute effects. The acute, oral LD$_{50}$s for PCP are: 120-180 mg/kg for the mouse, 27-100 mg/kg for the rat, 100 mg/kg for the guinea pig, 100 - 130 mg/kg for the rabbit, and 150 - 200 mg/kg for the dog (Christensen et al., 1974; Deichmann et al., 1942; Knudsen et al., 1974; McGavack et al., 1941; Stohlman, 1951. The acute symptoms of intoxication are vomiting, hyperpyrexia, elevated blood pressure, increased respiration rate, and tachycardia. The LD$_{50}$ after oral administration of PCP to male and female rats was 146 and 175 mg/kg and upon percutaneous exposure 320 and 330 mg/kg, respectively (Gaines, 1969).

Subchronic and chronic effects. In a study to determine the subchronic toxicity of the compound, PCP was fed in the diet to groups of Wistar rats at concentrations of 0, 25, 50, and 200 ppm for a 90-day period (Knudsen et al., 1974). Female rats receiving 200 ppm (10 mg/kg/day) PCP showed a reduced growth rate while liver weights were increased in male rats ingesting 200 and 50 ppm (2.5 mg/kg/day). After 6 weeks, rats fed 50 and 200 ppm PCP showed elevated hemoglobin and hematocrit values whereas at 11 weeks, hemoglobin and erythrocytes were significantly reduced in the same groups of animals. No PCP related effects were seen in animals fed 25 ppm (1.25 mg/kg/day). In another experiment, male rats received 1,000 ppm (50 mg/kg/day) of technical or pure PCP for a 90-day period (Kimbrough and Linder, 1975). Both PCP samples caused an increase in liver weight. Much more severe histopathological changes occurred in the livers of rats given the technical PCP than in those given the pure PCP. In another 90 day study, Sprague-Dawley rats showed increased liver and kidney weights, elevated serum alkaline phosphatase, and depressed serum albumin levels in animals consuming 3 mg/kg/day of technical PCP (Johnson et al., 1973). When a sample of improved PCP containing substantially reduced amounts of dioxins was fed to rats, no adverse effects were seen at 3 mg/kg/day. In animals receiving chemically pure PCP, kidney and liver weights were elevated at 30 and 10 mg/kg/day, respectively, but 3 mg/kg/day was without adverse toxicologic effect.

In a chronic study, liver weights were significantly increased in rats ingesting 500 ppm (25 mg/kg/day) technical PCP over an 8 month period (Kimbrough and Linder, 1975). No toxic effects were observed at 100 ppm (5.0 mg/kg/day) PCP.

When female weanling rats were fed pure or technical PCP for 8 months, increased urinary porphyrin excretion and increased liver porphyrin levels were observed in animals fed 100 (5.0

mg/kg/day) or 500 ppm of the technical product (Goldstein et al., 1976). None of the rats fed pure PCP became porphyric. Liver weights were increased in rats receiving 500 ppm (25 mg/kg/day) of technical PCP but were unchanged in animals fed 500 ppm of the pure phenol. Thus the porphyrin and other major liver changes induced by technical PCP are apparently due to contaminants, probably the chlorinated dibenzo-p-dioxins, rather than PCP.

Mutagenicity. PCP proved negative in the sex-linked lethal test in *Drosophila* (Vogel and Chandler, 1974).

Carcinogenicity. No available data.

Teratogenicity. In a study to examine the potential teratogenicity of PCP, purified and commercial grade PCP were administered to Sprague-Dawley rats on days 6 - 15, 8 - 11, and 12 - 15 of gestation (Schwetz et al., 1974). PCP was embryotoxic and fetotoxic at doses of the commercial and pure phenol of 15 mg/kg and above. The no adverse effect dose level was 5 mg/kg for the commercial PCP, but at this same dose level, delayed ossification of the skull was observed after treatment with pure PCP.

Oral administration of 0, 1.25, 2.5, 5, 10, and 20 mg/kg PCP to hamsters on days 5 - 10 of gestation produced fetal death and/or resorptions at 5 mg/kg/day and above (Hinkle, 1973).

III. CONCLUSIONS AND RECOMMENDATIONS

There are substantial disagreements in the results of several of the subacute and chronic toxicity experiments with PCP (Table 1), perhaps because of the use of inadequately characterized PCP preparations in these studies. In addition, two year chronic toxicity experiments in one or more species have not yet been conducted with this extensively used chemical. High doses (>5 mg/kg/day) of PCP have been shown to be teratogenic in rats and hamsters when administered during susceptible days of gestation. There is also a need for an adequate determination of the carcinogenic potential of this chemical.

On the basis of the available chronic toxicity data an ADI for pentachlorophenol has been calculated to be 0.003 mg/kg/day. The data and calculations are summarized in Table VI-55.

TABLE VI-55. Summary of Chronic Toxicity Data for Pentachlorophenol

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse effect Level or Lowest Minimal-effect Level	Effect Measured	Reference
Rat	12 weeks	0-200 ppm in diet, 20 animals per group	25 ppm (1.25 mg/kg/day)	No toxic effect	Knudsen *et al.*, 1974
Hamster	days 5-10	1.25-20 mg/kg/day orally	2.5 mg/kg/day	No fetotoxic or embryotoxic effects	Hinkle, 1973
Rat	90 days	0-30 mg/kg/day in diet[a]	3 mg/kg/day[e]	No toxic effect	Johnson *et al.*, 1973
Rat	90 days	0-30 mg/kd/day in diet[b]	3 mg/kg/day	Increased organ weights, serum enzyme changes	Johnson *et al.*, 1973
Rat	days 6-15	0-50 mg/kg/day, orally, 20-26 animals per group[a]	5 mg/kg/day	Teratogenic effects	Schwetz *et al.*, 1974
Rat	8 months	0-50 ppm in diet, 20 animals per group[b]	100 ppm (5.0 mg/kg/day)	No toxic effect	Kimbrough and Linder, 1975
Rat	8 months	0-500 ppm in diet[a]	500 ppm (25 mg/kg/day)	No toxic effect	Goldstein *et al.*, 1976

Using an uncertainty factor of 1,000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{3}{1,000} = 0.003 \text{ mg/kg/day (ADI)}, \quad 0.003 \times 70^{c} \times 0.1^{d} = 0.021 \text{ mg/liter.}$$

[a] pure pcp

[b] Technical pcp

[c] Assume average weight of human adult = 70 kg.

[d] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[e] Best study from which to calculate suggested no-adverse-effect level.

PHENYLACETIC ACID

I. INTRODUCTION

Phenylacetic acid is derived from benzyl cyanide. It is used in the manufacture of perfume, medicines, penicillin, fungicides, plant hormones, and flavorings (Chem. Dict. 1972). Phenylacetic acid is slightly soluble in cold water. Of the 10 water supplies surveyed by the EPA (1975a), only the finished water of Seattle contained phenylacetic acid, at 4 µg/liter. (NOMS, EPA 1975a).

II. METABOLISM

Phenylacetic acid and alkyl chloro derivatives are rapidly absorbed from human buccal tissues or membranes. Phenylacetic acid inhibits the activity of coenzyme A. At 0.5 - 1 mM/kg, it inhibits the acetylation of sulfanilamide (Lisunkin, 1965).

III. HEALTH ASPECTS

A. Observations In Man

The adverse health aspects of phenylacetic acid have not been examined in man.

B. Observations In Other Species

Acute effects. The oral LD_{50} of phenylacetic acid is 1,630 mg/kg in rats. In a study of the acute effects in mice, intraperitoneal injection of 300 mg/kg proved toxic; 11 of the 15 experimental animals died (Anderson *et al*., 1936). The time to death varied from 10 minutes to 10 days.

Chronic effects. No available data.

Mutagenicity. No available data.

Carcinogenicity. Hoshino (1970) reported that phenylacetic acid did not promote tumor formation when the compound was given to rabbits intravenously and subcutaneously for 40 days.

Teratogenicity. In a teratogenic study with rats, the administration of phenylacetic acid on the twelfth day of embryogenesis affected body weight, retarded skeletal ossification, and caused embryos to be resorbed at twice the rate of controls. The dosage was 0.2% of the LD_{50}, or 3.2 mg/kg (Anderson *et al*., 1936).

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity, and long term oral toxicity of phenylacetic acid, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

PHTHALIC ANHYDRIDE

I. INTRODUCTION

Phthalic anhydride is used in the manufacture of plasticizers, alkyl and polyester resins, synthetic fibers, dyes, pigments, pharmaceuticals, and insecticides (EPA, 1975d). The United States production of this compound in 1973 was over 1 billion pounds (USITC, 1975). It is soluble at 1 part in 162 parts of water (Merck Index, 1968). It has been detected in finished water (EPA, 1976).

II. METABOLISM

Phthalic anhydride is apparently excreted largely unchanged by both animals and man. In man and dogs, the unchanged compound can be recovered in urine almost quantitatively (Williams, 1959). There is no firm evidence that phthalic anhydride is converted to phthalic acid in the body; if it is, it should occur as the acid in urine.

III. HEALTH ASPECTS

A. Observations In Man

In man, phthalic anhydride is an eye, skin, and mucous-membrane irritant (Friebel, 1956; Merlevede and Elskens, 1957; Baader, 1955; Menshick, 1955; Chezzi and Scotti, 1965).

B. Observations In Other Species

Acute effects. Fassett (1963a) recorded the acute oral LD_{50} as 800 - 1,600 mg/kg in rats and less than 100 mg/kg in guinea pigs. Vapor exposures, particularly to heated phthalic anhydride, produced congestion, irritation, and injury of lung cells (Friebel, 1956). Jacobs et al. (1940) reported that the compound sensitized the skin of guinea pigs. Freibel (1956) reported a study in which oral doses in rats (starting at 20 mg/kg/day) were doubled weekly; 0.89 g/kg was reached by the ninth week. Rats that died at the high dosage had severe nephrosis, with destruction of the tubular epithelium. Surviving animals had gastric ulceration.

Chronic effects. No available data.

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity, and long term oral toxicity of phthalic anhydride, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

POLYCHLORINATED BIPHENYLS

I. INTRODUCTION

Polychlorinated biphenyls (PCB's) are mixtures of chlorinated biphenyls produced commercially by the chlorination of biphenyl. PCB's are used in the production of capacitors and transformers.

PCB's are highly persistent and can accumulate in the environment. They are soluble in water at 0.04 - 0.2 ppm. Trichlorinated, tetrachlorinated, and pentachlorinated biphenyls have been detected in a few water supplies: at 3.0 μg/liter in Winnebago, Illinois, and 0.1 μg/liter in Sellersberg, Indiana (EPA, 1975b).

II. METABOLISM

Oral feeding of a single dose of PCB's to rodents and rhesus monkeys has shown that intestinal absorption is rapid and 90% complete (Albro and Fishbein, 1972; Allen and Norback, 1976, Berlin *et al.*, 1973). The feces provide the major route of excretion; only traces of PCB's could be found in the urine of the animals. When the analysis of feces is limited to the determination of unchanged PCB's, the recovery of the administered dose is incomplete (Platonow *et al.*, 1972).

Berlin *et al.* (1975a,b) demonstrated that after a single oral dose of a $[^{14}C]$pentachlorobiphenyl, radioactivity rapidly entered the circulation and was distributed in the tissues, particularly in liver, kidneys, lungs, and adrenals; within 24 h, it had migrated to the fat, which remained the major reservoir of unchanged PCB's in the body, until only traces remained after 32 days.

The degradation and elimination of PCB congeners appear to take place via the hepatic microsomal enzyme system. Two possible mechanisms for biotransformation have been suggested by Ecobichon (1976). The first and most rapid mechanism involves the formation of an arene oxide intermediate and requires the presence of unsubstituted adjacent carbon atoms in the nucleus. The second and much slower uses a different hydroxylation system for isolated unsubstituted positions, as are found in highly chlorinated biphenyls. Two adjacent unsubstituted carbon atoms appear to be important in metabolism, in that their presence facilitates the formation of arene oxides by the hepatic mixed-function oxidases.

Polychlorinated biphenyls are known to be strong inducers of hepatic mixed-function oxidase enzymes. The potency increases with increasing chlorination of the biphenyl rings. The PCB's are somewhat unique in this regard in that they induce both type I and Type II P-450, but this may be due in part to contaminants in the PCB's tested (HEW, 1976).

These effects raise a concern that such induction may increase metabolism of birth control hormones with possible harmful effects. Also to be considered is the possibility that environmental carcinogens may be activated at a faster rate (HEW, 1976).

III. HEALTH ASPECTS

A. Observations in Man

PCB's are liver toxins and cause chloracne and possibly peripheral neuropathy in man (Murai and Kuroiwa, 1971).

There is no information on acute adverse effects on humans. Although Yusho disease (an acute outbreak of disease which occurred in Japan) has generally been ascribed to the ingestion of PCB's in rice oil (0.07 mg/kg/day for at least 50 days), recent evidence provided by Kuratsune et al. (1976) suggests that the rice oil was contaminated with polychlorinated dibenzofurans (PCDF's). These compounds may have played a significant role in the observed toxicity. Initial measurements of the concentrations of PCDF's in the PCB's suggested that these materials contributed at least as much to the toxicity as the PCB's themselves. Symptoms included excessive fatigue, headache, phymata in articular regions, fever, cough, digestive disturbances, numbness, and menstrual disorders. Physical signs consisted primarily of cutaneomucosal abnormalities, such as acneiform eruptions and black comedones on face, buttocks, and intertriginous sites; increased pigmentation of face, palpebral conjunctiva, gingiva, and nails; ocular signs consisting of swelling and hypersecretion of the meibomian gland and palpebral edema.

Recent surveys have indicated that PCB can be found in the milk of nursing mothers. The highest reported level was 10.6 ppm with a mean of 1.8 ppm for all samples (HEW, 1976).

This information is especially meaningful in light of Allen's recent work (1975). Female rhesus monkeys orally exposed to 2.5 and 5.0 ppm of PCB (Aroclor 1248) developed facial acne, erythema, subcutaneous edema conjunctivitis and loss of eyelashes. All infants born to PCB exposed mothers had PCB's in their tissues at birth. These infants also developed skin lesions as a result of nursing PCB contaminanted milk. Fifty percent of the infants died within 4 months.

B. Observations in Other Species

__Acute effects__. Oral LD_{50}'s of several Arochlor's (a trade name in which the last two digits indicate the percent chlorination) agents have been determined in rats: Arochlor 1240, 4.25 g/kg (Bruckner et al., 1973); Arochlor 1254, 1.3 - 2.5 g/kg (Grant and Philips, 1974); Arochlor 1256, 4 - 10 g/kg in female Sherman rats (Kimbrough et al., 1972); and Arochlor 1254 and 1260, 1,295 and 1,315 mg/kg, respectively, in weanling rats (Kimbrough, 1974).

__Subchronic and chronic effects__. Tucker and Crabtree (1970) reported deaths in rats fed Arochlor 1 g/kg for 28-53 days. Repeated daily oral administration of 300 mg of Aroclor 1221, 1242, or 1254 in rabbits for 14 weeks produced liver enlargement and damage and one death with Aroclor 1254, but only minor changes with Aroclor 1221 (Koller and Zinkl, 1973). Allen et al. (1974) administered Aroclor 1248 at 25 mg/kg of diet to six female rhesus monkeys for 2 months, with production of facial edema, loss of hair, and acne a month after onset of feeding. Mink on diets containing PCB at 30 mg/kg (Aroclor 1242, 1248, and 1254 at 10 mg/kg each) demonstrated 100% mortality within 6 months (Aulerich et al., 1973). Female mink fed a diet supplemented with Aroclor 1254 at 5 mg/kg for 9 months failed to produce offspring (Ringer et al., 1972).

The oral administration of Aroclor 1242, 1254, and 1260 in rats for 18 months at 1, 10, and 100 mg/kg (Keplinger et al., 1971) produced adverse effects only at 100 mg/kg. With Aroclor 1242 and 1254, there was an increase in liver weight and a reduction in litter survival at 100 mg/kg. Kimbrough et al. (1972) reported experiments in which male rats survived Aroclor 1260 at 1 g/kg for 8 months, but eight of 10 females died at this dosage. With both Aroclor 1254 and 1260, there was a significant dose-dependent increase in liver weight in male rats down to 20 mg/kg in the diet; in female rats, liver enlargement occurred only at 500 mg/kg and higher.

The rhesus monkey is the only animal reported to show signs of poisoning similar to those seen in Yusho patients. Oral administration of Aroclor 1248 at 2.5 and 5.0 mg/kg produced periorbital edema, alopecia, erythema, and acneiform eruptions within 1 - 2 months. At 25 mg/kg, one of six died; at 100 and 300 mg/kg, the mortality approached 100% in 2 - 3 months. Survivors still showed signs of poisoning 8 months after exposure was discontinued (Allen and Norback, 1973; Allen et al., 1974; Allen, 1975).

__Mutagenicity__. Aroclor 1242 and Aroclor 1254 have not been found to have mutagenic potential when administered in rats as

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single or repeated large daily doses (Green et al., 1975), when assessed by cytogenetic analysis of bone marrow and spermatogonia.

Carcinogenicity. There have been a number of carcinogenicity studies with mice and rats treated with combinations of PCB's. Only the study of Kimbrough et al. (1975) provided a true long-term chronic feeding study. They fed Sherman female rats Aroclor 1260 at 100 mg/kg in their diets for 21 months and sacrificed them at 23 months. At this dosage, 26 of 184 in the experimental group and one of 173 in the controls had hepatocellular carcinomas.

Teratogenicity. One study (Kato et al., 1972) demonstrated that PCB's could cross the placenta but produced no defects. Other studies (Funatsu et al., 1972; Miller, 1971) have linked maternal ingestion of PCB with dark-brown staining of the skin of newborn babies.

IV. CARCINOGENIC RISK ESTIMATES

Only the study by Kimbrough et al. (1975) is of sufficient duration to permit a statistical extrapolation of risk to man. The available set of dose response data was considered as described in the risk section in the chapter on margin of safety. The set of dose response data was used to statistically estimate both the lifetime risk and an upper 95% confidence bound on the lifetime risk at the low-dose level. These estimates are of lifetime human risks and have been corrected for species conversion on a dose per surface area basis. The risk estimates are expressed as a probability of cancer after a lifetime consumption of 1 liter of water/day containing Q ppb of the compound of interest. For example, a risk of 1×10^{-6} Q implies a lifetime probability of 2×10^{-5} of cancer if 2 liters/day were consumed and the concentration of the carcinogen was 10 ppb (i.e., Q=10). This means that at a concentration of 10 ppb during a lifetime of exposure this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the United States is taken to be 220 million people this translates into 4,400 excess lifetime deaths from cancer or 62.8/year. For the PCB Arochlor 1260 at a concentration of 1 µg/liter (Q=1) the projected risk for man is 2.2×10^{-6} Q. The upper 95% confidence estimate of risk at the same concentration is 3.1×10^{-6} Q.

It should be noted that this extrapolation is based on a one hit mathematical model which may be invalid for this chemical. In addition, the extrapolation pertains to Arochlor 1260 and not to any of the polychlorinated biphenyls which make up this compound. It would be impossible from this limited study to single out any one of the PCB's as the carcinogenic agent and it should be kept in mind that they may be acting synergistically.

V. CONCLUSIONS AND RECOMMENDATIONS

Although there are considerable data on toxicity of mixtures of PCB's, there is a paucity of data on the pure congeners present in these mixtures. Whether chronic toxicity is related to the metabolism of the PCB's and their intermediates or to the highly chlorinated stored PCB's remains to be determined. Considerably more attention must be directed to the detection of impurities in PCB's at very low concentrations. Polychlorodibenzofuran may constitute only one of several significant contaminating compounds responsible for PCB toxicity. Populations at special risk--both the industrially exposed and those heavily exposed by the ingestion of contaminated foods--should be carefully evaluated.

Despite the current lack of evidence in the United States that dietary PCB's have any deleterious effects on health, there is a growing concern with long-range effects of the contamination of our ecosystem with these chemicals. There is an urgent need for epidemiologic studies of exposed populations, more precise identification of all sources of PCB contamination, and efforts directed at the control of disposal of PCB's. Because of the demonstrated carcinogenic potential, studies on individual congeners, both those metabolized and those stored by man, are urgent.

The available chronic toxicity data are summarized in Table VI-56.

TABLE VI-56. Summary of Chronic Toxicity Data for PCB's

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse effect Level or Lowest Minimal-effect Level	Effect Measured	Reference
Mink	6 mo.		30 mg/kg in diet	100% mortality	Aulerich et al., 1973
Mink	9 mo.		5 mg/kg in diet	Females failed to produce offspring	Ringer et al., 1972
Rat	18 mo.	1,10,100 mg/kg	100 mg/kg in diet	Adverse effects	Keplinger et al., 1971
Rat (Female)	21 mo.	0,100 mg/kg in diet 173-184 animals/group (Aroclor 1260)	100 mg/kg	Hepatocellular carcinoma	Kimbrough et al., 1975

[Aroclor 1260 is an animal carcinogen]

PROPYLBENZENE

I. INTRODUCTION

Propylbenzene (1-phenylpropane) is produced in petroleum refining and as a byproduct of cumene manufacture. It is used in the manufacture of methylstyrene and in textile dyeing (EPA, 1975d). It is insoluble in water (CRC Handbook of Chem. & Phy., 1970-1971). Two of the 10 water supplies surveyed by the EPA (1975a) contained propylbenzene in the finished water, at 0.05 µg/liter in Miami and 0.01 µg/liter in Cincinnati.

II. METABOLISM

Propylbenzene is probably readily absorbed from the gastrointestinal tract and the lungs and excreted mainly in the urine of humans (Thienes and Haley, 1972). No information on tissue or organ storage was available. Metabolically, propylbenzene is characterized by high stability of the benzene nucleus (Smirnova and Stepanova, 1969). In rats, there appears to be a dual metabolic pathway: side-chain oxidation and ring hydroxylation, with the former preferred (Gerarde and Ahlstrom, 1966).

III. HEALTH ASPECTS

A. Observations in Man

Propylbenzene is irritating to the mucous membranes, eyes, nose, throat, and skin. Systemically, it causes depression of the central nervous system, headache, anorexia, muscular weakness, incoordination, nausea, vertigo, paresthesias, mental confusion, and unconsciousness. Possible effects on the liver, bone marrow, and heart are not known (Thienes and Haley, 1972).

B. Observations in Other Species

Acute effects. In one study, the LD$_{50}$ was 7.5 g/kg in rats and 5.2 g/kg in mice (Smirnova and Stepanova, 1969). In another study, the LD$_{50}$ in rats was shown to be 6.04 g/kg (Jenner *et al.*, 1964).

Chronic effects. In a 6-month subchronic oral study (Gerarde and Ahlstrom, 1966), groups of 15 rabbits were fed propylbenzene at 0.25 and 2.5 mg/kg/day. The test animals did not differ from the controls in general appearance, body weight, organ weights, and protein function of the liver. There was a 7% decrease in the red-cell count in the high-dosage group that was not significant. Hemosiderin was deposited in the spleens of the high-dosage animals, indicating red-cell destruction. There was a nonsignificant leukocyte increase in both dosage groups. Individual animals exhibited mild protein dystrophy of the liver and kidneys.

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity and long term oral toxicity of propylbenzene, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

STYRENE

I. INTRODUCTION

Styrene monomer is synthesized from ethylene and benzene. It is used in the manufacture of polystyrene plastics, resins, insulators, synthetic rubber, and protective coatings (Chem. Dict. 1972). The United States production of styrene in 1973 was over 2.56 billion pounds (USITC, 1975). Styrene is insoluble in water. It has been detected in the finished water of three of the 10 water supplies surveyed by the EPA, (1975a).

II. METABOLISM

In a study conducted by El Masri *et al.* (1958), rabbits were given styrene orally, and the metabolites were determined. It was established that the main metabolite of styrene was hippuric acid, which accounted for 30 - 40% of the oral dose. Lesser metabolites were mandelic acid and phenylglycol, the latter being excreted as a monoglucuronide. Only about 2% of the styrene administered was eliminated unchanged in the expired air. Because phenylglycol itself yields hippuric acid, mandelic acid, and phenylglycol as metabolites, it is suggested that styrene may undergo perhydroxylation *in vivo* to its intermediate, phenylglycol. It was noted that the metabolites of styrene were almost completely excreted 1 - 2 days after administration of the single dose.

III. HEALTH ASPECTS

A. Observations in Man

Wolf *et al.* (1956), in the course of conducting inhalation studies on animals, exposed human subjects to various concentrations of styrene monomer. They reported very strong odor with eye and nasal irritation at 600 ppm, detectable odor with no irritation at 60 ppm, and no detectable odor at 10 ppm and less.

Stewart *et al.* (1968) exposed human volunteers to styrene vapors at approximately 50, 100, 200, and 375 ppm for periods of 1 - 7 h. Only at 375 ppm did the subjects experience subjective symptoms and objective signs of transient neurologic impairment. The vapors irritated the eyes and nose and in one subject produced a burning sensation of the facial skin. Neurologic effects were manifested by inability to perform a normal modified Romberg test, a decrease in the Crawford Manual Dexterity color and Pin Test score, and decreased performance on the Flannigan Coordination Test. Stewart *et al.* (1968) showed that the amount of styrene exhaled after an exposure indicated the extent of exposure. Urine hippuric acid content, however, was not a sensitive indicator.

B. Observations in Other Species

Acute effects. In an acute study, Spencer et al. (1942) exposed rats and guinea pigs to various vapor doses of the compound. At the lowest dose (650 - 1,300), the animals demonstrated eye and nose irritation. Styrene could be tolerated for only 8 h at 1,300 - 2,000 ppm. The maximal tolerated time without serious adverse effects was reduced to 1 h at 2,500 ppm; and 10,000 ppm proved lethal in 30 - 60 m.

Chronic effects. In a study of the chronic effects of styrene, Spencer et al. (1942) intubated rats 5 days/week for 28 days at 2.0, 1.0, 0.5, and 0.1 g/kg/day. Animals survived 0.5 g/kg, but lost weight, probably owing to gastrointestinal irritation. The no-adverse-effect dosage was 0.1 g/kg/day. Wolf et al. (1956) intubated rats daily, 5 days/week, for 185 days (132 doses), at doses of 66.7, 133, 400, and 667 mg/kg/day. The no-adverse-effect level was 133 mg/kg/day. The only dosage-related effects at higher dosages were increased liver and kidney weights. In the same study, rats, guinea pigs, rabbits, and monkeys were chronically exposed to styrene by inhalation. The no-observed-adverse-effect concentration was 650 - 1,300 ppm, with some species variability.

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

Styrene at high concentrations is mainly an irritant whether ingested or inhaled. Humans have tolerated acute exposures of 200 ppm with no ill effects.

An ADI was calculated on the basis of the available chronic toxicity data. Based on this data the ADI is 0.133 mg/kg/day. The available chronic toxicity data and calculations are summarized in Table VI-57.

TABLE VI-57. Summary of Chronic Toxicity Data for Styrene

Species	Duration of study	Dosage levels and No. of Animals per Group	Highest No-adverse effect level or lowest Minimal-effect level	Effect Measured	Reference
Rat	28 days	0-2.0 g/kg/day, intubated	0.1 g/kg/day	No adverse effect	Spencer *et al.*, 1942
Rat	185 days	0-667 mg/kg/day, intubated	133 mg/kg/day[c]	No adverse effect	Wolf *et al.*, 1956

Using an uncertainty factor of 1,000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{133}{1,000} = 0.133 \text{ mg/kg/day (ADI)}, \quad 0.133 \times 70^{a} \times 0.1^{b} = 0.9 \text{ mg/liter}.$$

[a] Assume average weight of human adult = 70 kg.

[b] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[c] Best study from which to calculate suggested no-adverse effect level.

1,1,1,2-TETRACHLOROETHANE

I. INTRODUCTION

1,1,1,2-Tetrachloroethane is used as a solvent and in the manufacture of insecticides, herbicides, soil fumigants, bleaches, paints, and varnishes (EPA, 1975d). It is soluble in water at 1 g in 350 ml at 25 C. It is potentially formed during chlorination of water (EPA, 1975d). It has been reported that the finished water of the District of Columbia contained tetrachloroethane at 1 μg/liter (Scheiman et al., 1974) and that of New Orleans, 0.11 μg/liter (EPA 1974).

II. METABOLISM

Truhaut (1973) reported that 1,1,1,2-tetrachloroethane underwent hydrolytic dehalogenation in rats, guinea pigs, and rabbits; this resulted in the formation of trichloroethanol, which was eliminated primarily in the urine in the form of a conjugated glucuronic derivative (urochloralic acid). Oxidation into trichloroacetic acid was considerable only in rats. The only halogenated compound found in expired air was untransformed 1,1,1,2-tetrachloroethane.

In a study of the metabolism of 1,1,1,2-tetrachloroethane in mice, Yllner (1971a,b) administered the compound subcutaneously at 1.2 - 2.0 g/kg and followed the excretion in urine for 3 days. About half the dose (21 - 62%) was expired and unchanged. The part metabolized was excreted mainly as trichloroethanol (17 - 45% of the dose) and to a lesser extent as trichloroacetic acid (1 - 7%).

It is concluded that the metabolism of tetrachloroethane probably takes place mainly via a staged hydrolytic fission of carbon-chlorine bonds and oxidation to give first dichloroacetic acid and then glyoxylic acid. With part of the tetrachloroethane, a nonenzymic dehydrochlorination occurs, with the formation of trichloroethylene, which is also found in the breath. Trichloroethylene is probably the precursor of the trichloroethanol and trichloroacetic acid found in the urine.

III. HEALTH ASPECTS

A. Observations In Man

Minot and Smith (1921), cited by Parmenter, discovered the high percentage of large mononuclear cells found in the circulating blood of patients suffering from the early stages of tetrachloroethane poisoning. These findings were confirmed by Parmenter (1923), who observed that, during the appearance of early tolerance to tetrachloroethane fumes, its toxicity was measured best by the appearance of the differential count of the blood, which often went as high as about 30 - 40% in large mononuclear cells without clinical signs of disease. Parmenter listed the symptoms as occasional complaints of a tired feeling and, more often, gastric symptoms, such as lack of appetite and slight nausea, possibly a slight headache, and intercurrent remissions and exacerbations that caused absenteeism. He stated that a high mononuclear-cell count (20% or above) usually indicated poisoning, although this varied with individual tolerance. A large number of broken cells of this type indicated rapid progression of poisoning, in his opinion. McNally's (1937) observations of industrial exposures agreed with the clinical observations of the foregoing authors.

In a study of 380 workers employed in the manufacture of bangles in small factories in India, Lobo-Mendonca (1963) tried to determine the degree of inhalation of tetrachloroethane that formed part of the environment of workers engaged in washing and handling bangles and production machinery around or in which tetrachloroethane was used as a cleaning agent. Interest centered on the high percentage of workers with nervous symptoms, such as headache, vertigo, nervousness, numbness, and tremors. Tetrachloroethane at 9 - 17 ppm induced tremors in 14% of the personnel; at 40 - 74 ppm, in 33%; at 50 - 61 ppm, in 41%; and at 65 - 98 ppm, in 50%.

B. Observations In Other Species

Acute effects. The oral LD_{50} of 1,1,1,2-tetrachloroethane was 800 mg/kg in rats and 1,500 mg/kg in mice (Truhaut et al., 1974). Compared with 1,1,2,2-tetrachloroethane, 1,1,1,2-tetrachloroethane was one-half or one-third as toxic, but had hepatotoxic properties, which were dose-related, in different animal species. It induced microvacuolization or central lobular necrosis or both in the liver. It also passed through the placental barrier and affected the fetus.

Chronic effects. In a study of the effects of chronic action of low concentrations of chlorinated hydrocarbons on the production of various classes of immunoglobulins, Shmuter (1972) used rabbits that inhaled chlorinated hydrocarbons at 2 mg/m³ for 3 h/day for 8 - 10 months. Tetrachloroethane was found to be more harmful to total antibody formation than its pentachloro- or dichloro- analogues.

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity, and long term oral toxicity of 1,1,1,2-tetrachloroethane, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

TETRACHLOROETHYLENE

I. INTRODUCTION

Tetrachloroethylene (perchloroethylene) is used as solvent, heat-transfer medium, and in the manufacture of fluorocarbons (EPA, 1975d). The United States production of this compound in 1973 was over 705 million pounds (USITC, 1975). It is insoluble in water (CRC Handbook of Chem. & Phys., 1970-1971). During chlorination of water treatment, it can be formed in small quantities (EPA, 1975d). It has been found in the finished water of the New Orleans area at up to 5 μg/liter (EPA, 1974). Eight of the 10 water utilities surveyed by the EPA (1975a) contained tetrachloroethylene, at 0.07 - 0.46 μg/liter.

II. METABOLISM

There have been a number of studies pertaining to the metabolism of tetrachloroethylene in mice, rats and humans (Yllner, 1961; Daniel, 1963; Ogata, 1971). The consensus appears to be that most of the material is expired unchanged and that very little (5%) is metabolized and later excreted in the urine or feces. However, experience with similar compounds indicates that the portion metabolized may be markedly greater at low doses than at high doses. Up to 10% remains in the body (very likely in the fat) after 4 days, but, to judge by these reports there is little likelihood of cumulative toxicity.

III. HEALTH ASPECTS

A. Observations in Man

Rowe *et al.* (1952) showed central nervous system effects in man from single exposures at 200 ppm, but not at 100 ppm.

B. Observations in Other Species

Acute effects. In studies of the acute effects of tetrachloroethylene, the oral LD_{50} was shown to be 4,000 mg/kg in dogs and 5,000 mg/kg in rabbits (Registry of Toxic Effects of Chemical Substances, 1975).

Chronic effects. In a chronic study, Rowe *et al.* (1952) exposed groups of rats, rabbits, guinea pigs, and monkeys repeatedly to various concentrations of tetrachloroethylene (100 - 2,500 ppm) for various periods (13 - 179 exposures in 18 - 250 days). No adverse effects were observed at 100 ppm.

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. Schwetz et al. (1975) examined the teratogenic effects of tetrachloroethylene in rats and Swiss Webster mice. The animals were exposed at 300 ppm 7 h/day on days 6 - 15 of gestation. There was no significant maternal, embryonal, or fetal toxicity, nor was tetrachloroethylene teratogenic in either species.

IV. CONCLUSIONS AND RECOMMENDATIONS

Tetrachloroethylene is not teratogenic in one strain of rats and mice. In view of the relative paucity of data on the mutagenicity, carinogenicity, and long term oral toxicity of tetrachloroethylene, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before final limits in drinking water can be established.

TOLUENE

I. INTRODUCTION

Toluene is formed in petroleum refining and coal tar distillation. It is used in the manufacture of benzene derivatives, caprolactam, saccharin, perfumes, dyes, medicines, solvents, TNT, and detergent and as a gasoline component (EPA, 1975d). The United States production of toluene in 1973 was over 6.8 billion pounds (USITC, 1975). It is insoluble in water (CRC Handbook of Chemistry and Physics, 1970-1971). Six of the 10 water supplies surveyed by the EPA (1975a) contained toluene. It has been reported that the finished water of the New Orleans area contained toluene, at up to 11 µg/liter (EPA 1975c).

II. METABOLISM

In man and rabbits, Bakke and Scheline (1970) reported that approximately 80% of a dose of toluene was excreted in the urine as hippuric acid (benzoyl glycine), whereas most of the remainder was exhaled (Williams, 1959). These authors also reported that 0.4 - 1.1% was excreted as o- or p-cresol. In hydrolysed urine, small amounts of benzyl alcohol were detected; this suggested that this may be an intermediate in the formation of benzoic acid.

Pretreatment of rats with phenobarbital increased the rate of disappearance of toluene from the blood (Ikeda and Ohtsuji, 1971) and shortened the sleeping time after injection of toluene; thus, induction of the hepatic microsomal enzyme system may stimulate toluene metabolism.

The reports of Ogata *et al.* (1970, 1971) tend to show that, at relatively low exposures to toluene, the excretion of hippuric acid is proportional to the exposure. They also demonstrated that, when human volunteers were exposed at up to 200 ppm, 68% of a calculated dose was excreted as hippuric acid.

III. HEALTH ASPECTS

A. Observations in Man

All the available information on acute human exposure to toluene suggests a narcotic effect. Benzoic acid and hippuric acid, the major metabolites of toluene, are relatively innocuous and have been used as a clinical measure of liver function. In these studies, subjects are given 6 g of sodium benzoate orally, and excretion of hippuric acid is measured over the next 4 h. Excretion over this period accounts for approximately 50% of the ingested dose. Thus, relatively large quantities of the known major metabolites produce no known toxic effects in man. In addition, benzoic acid is approved as an antimicrobial food additive at 1,000 ppm.

Many reports on long-term industrial exposure to toluene are available. Capellini and Alessio (1971) reported that 17 workers were exposed for several years to a mean atmospheric toluene concentration of 125 ppm, without any detectable change in blood characteristics or in liver function. Banfer (1961) reported on studies of 889 photogravure printers and helpers exposed for more than 3 years to variable toluene concentrations (measured on only 1 day, maximal concentration was 400 ppm; generally, it was 200 ppm), with no hematologic abnormalities. Greenburg (1942) reported on 61 workers exposed to toluene at 100 - 1,100 ppm from 2 weeks to 5 years. He reported no severe illness, but found some evidence of mild red-cell decrease, enlarged liver, and increased mean corpuscular hemoglobin concentration.

Forni et al. (1971) reported that people exposed to toluene (at approximately 200 ppm) for work periods of 3 - 15 years showed a somewhat higher average rate of unstable chromosomal changes and calculated breaks, but the differences were not statistically significant.

The human exposure data suggest that some effects of narcosis are evident at around 200 ppm. This was the threshold limit value (TLV) suggested for control of industrial exposures from 1947 to 1971. The TLV was then lowered to 100 ppm, on the basis of irritation to eyes and upper respiratory tract. The NIOSH criteria document (1973) for a recommended standard for toluene indicated that a literature search failed to confirm any clinical or laboratory evidence of altered liver function in workers exposed to 80 - 300 ppm for many years.

B. Observations in Other Species

Acute effects. Svirbely et al. (1943) reported the minimal lethal acute inhalation concentration of toluene (containing 0.01% benzene) to be 20 mg/liter (5,300 ppm) in mice for a single 8-h exposure.

Chronic effects. Fabre et al. (1955) reported that two dogs chronically exposed for 8 h/day, 6 days/week, for 4 months to toluene (containing 0.1% benzene) at 2,000 ppm (7.5 mg/liter) and an additional 2 months at 2,660 ppm (10 mg/liter) showed signs of nervous system intoxication, incoordination, and paralysis of the hindlegs. Blood and bone marrow studies yielded normal results. Congestive changes were seen in lungs, heart, liver, kidneys, and spleen. Takeuchi (1969) exposed rats to toluene (99.9%) vapor at

200, 1,000, and 2,000 ppm for 6 h/day for 32 weeks. No significant changes in body weight or hematologic findings were reported.

Gerarde (1956) reported that rats given daily injections of toluene at 1 ml/kg in olive oil for 2 weeks showed no abnormalities with respect to peripheral blood, femoral bone marrow, or weight of thymus or spleen. In rabbits given toluene subcutaneously at 100 mg/kg/day for 6 weeks or 700 mg/kg/day for 9 weeks, no decrease in bone marrow function was found, as measured by uptake of tritium-labeled thymidine, nor was there any alteration in the formed elements of the peripheral blood.

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

Other than central nervous system depression, the inhalation of toluene at less than 2,000 ppm has produced no adverse effects. In addition, the major metabolite of toluene, benzoic acid, is considered relatively nontoxic and is an approved food additive.

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity and long-term oral toxicity of toluene, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before final limits in drinking water can be established.

TRICHLOROBENZENE

I. INTRODUCTION

Trichlorobenzene is produced by chlorination of monochlorobenzene. It is used as a solvent, dielectric fluid, lubricant, and heat-transfer medium; in polyester dyeing, and in termite preparations (EPA, 1975d).

The United States production of 1,2,4-trichlorobenzene in 1973 was over 28 million pounds (USITC, 1975). It is insoluble in water (CRC Handbook of Chemistry and Physics, 1970-1971). Trichlorobenzene can be formed in small quantities during chlorination of drinking water (EPA, 1975d). Of the 10 water supplies surveyed by the EPA (1975a), trichlorobenzene was only detected in the finished water of Lawrence, Massachusetts.

II. METABOLISM

In metabolic studies with rabbits using each of the three isomeric trichlorobenzenes at 0.5 g/kg, 1,2,3-trichlorobenzene was the most rapidly metabolized, and 1,3,5-trichlorobenzene was least rapidly metabolized. In 5 days, 62% of the 1,2,3-trichloro isomer underwent glucuronic conjugation. The major metabolite was 2,3,4-trichlorophenol; small amounts of 3,4,5-trichlorophenol, 3,4,5-trichlorocatechol, and mercapturic acid were also detected. 1,3,5-Trichlorobenzene formed practically no ethereal sulfate or mercapturic acid, and the only phenol formed was 2,4,6-trichlorophenol (Jondorf et al., 1955).

Along with tests on other halogenated benzenes, 1,3,5-trichlorobenzene was administered orally to rats at 2 mg/kg, and this chemical was found in the fat at greater concentrations than in liver, kidneys, heart, or blood. These studies were designed to show the possible effects of chlorinated substances from Rhine River water and how they might affect body burden in animal tissues and organs (Jacobs et al., 1974).

III. HEALTH ASPECTS

A. Observations In Man

In one plant where benzene was chlorinated over a period of 4 years, there was no apparent serious illness, liver function change, or alteration in blood components. One worker who inhaled a massive amount of trichlorobenzene experienced some hemorrhaging in the lungs (Erlicher, 1968).

B. Observation In Other Species

Acute effects. Acute-toxicity tests have been conducted in rats (CFE strain) and mice (CF No. 1 strain) by oral and percutaneous administration. The single-dose acute oral LD_{50} was 756 mg/kg in rats. The main signs of intoxication were decrease in activity at a low dose and convulsions at higher doses. Death occurred 5 days after exposure. The single-dose acute oral LD_{50} was 766 mg/kg in mice. Signs of intoxication were the same as in rats (Brown et al., 1969).

Chronic effects. In chronic-skin-irritation studies with rabbits and guinea pigs, trichlorobenzene was not irritating, although some degreasing action took place after prolonged contact. After 3 weeks of exposure, there was some skin inflammation characterized by spongiosis and parakeratosis. Livers of guinea pigs were found to have necrotic foci (Brown et al., 1969). Trichlorobenzene was also evaluated for its acnegenic potential in rabbits by applying 1,2,4-trichlorobenzene to the ears of rabbits for 13 weeks. There was no typical acneiform dermatitits, but there was some dermal irritation (Powers et al., 1975).

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity and long term oral toxicity of trichlorobenzene, estimates of the effects of chonic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

1,1,2-TRICHLOROETHANE

I. INTRODUCTION

1,1,2-Trichloroethane (Vinyl trichloride) is used as solvent for fats, oils, waxes, and resins and in the synthesis of organic chemicals(EPA, 1975d). It is insoluble in water(CRC Handbook of Chem. & Phys., 1970-1971). During chlorination water treatment, 1,1,2-trichloroethane can be formed in small quantities (EPA, 1975d). Of the 10 water supplies surveyed by the EPA (1975a), only the finished water of Miami contained 1,1,2-trichloroethane. It has also been found in the finished water of the New Orleans area, at less than 0.1 to 8.5 μg/liter (EPA, 1975c).

II. METABOLISM

Trichloroethane is excreted primarily by the lungs, with some elimination via the kidneys (Browning, 1965). The major metabolite in the mouse of this compound is chloroacetic acid; minor metabolites are 2,2-dichloroethanol, 2,2,2-trichloroethanol, oxalic acid, and trichoroacetic acid (Yllner, 1971a). In vitro, the compound is dechlorinated by a reconstituted rat liver microsomal mixed-function oxidase system (Gandolfi and Van Dyke, 1973).

III. HEALTH ASPECTS

A. Observations In Man

The adverse health aspects of this compound in man have not been examined. No toxic effects have been recorded in association with its applications in industrial solvents (Browning, 1965).

B. Observations in Other Species

Acute effects. LD$_{50}$'s of 1,1,2-trichloroethane were calculated to be: 0.58 (0.47 - 0.71) and 1.14 g/kg orally in rats (Smyth et al., 1969; Union Carbide Corp., 1968); 0.35 (0.28 - 0.44) ml/kg and 1.7 (1.0 - 4.7) ml/kg intraperitoneally in male and female Swiss-Webster mice, respectively (Klaassen and Plaa, 1966; Gehring, 1968); and 3.73 (3.30 - 4.21) ml/kg dermally in rabbits (Smyth et al., 1969; Toxicology Information Bulletin, 1968).

The hepatotoxicity of trichloroethane has been extensively examined in a variety of experimental animals. Cellular infiltration, vacuolation of hepatocytes, increased serum glutamic pruvic transaminase (SGPT) and prolonged retention of BSP (bromsulphalein) have been observed in studies with mice

(Klaassen and Plaa, 1966). SGPT increases and the threshold doses have also been shown to be potentiated by isopropyl alcohol and acetone in mice treated with 1,1,2-trichloroethane at 0.05 - 0.14 ml/kg (Traiger and Plaa, 1974). In dogs, mild centrilobular necrosis, slight subcapsular necrosis, and vacuolation of the centrilobular hepatocytes have been observed, in combination with increased SGPT (Klaassen and Plaa, 1967).

In studies that sought to examine the nephrotoxicity of trichloroethane, the presence of hyaline droplets, nuclear pycnosis, hydropic degeneration, increased eosinophilia, tubular necrosis with karyolysis, and loss of epithelium of convoluted tubules in mice have been reported, in combination with a decrease in p-aminohippuric acid concentration and altered urinary PSP (phenolsulfonphthalein) excretion (Klaassen and Plaa, 1966). In dogs, tubular necrosis has been observed after exposure to trichloroethane, but it appeared to be less severe than that seen in mice; urinary PSP excretion was also modified in dogs (Klaassen and Plaa, 1967).

Chronic effects. No available data.

Mutagenicity. No available data.

Carcinogenicity. There are some indications that responses to trichloroethane are comparable both qualitatively and quantitatively with those to carbon tetrachloride (Browning, 1965).

Teratogenicity. No available data.

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity and long term oral toxicity of 1,1,2-trichloroethane, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

TRICHLOROETHYLENE

I. INTRODUCTION

Trichloroethylene (trichloroethene) is used primarily in metal degreasing. It is also used in dry-cleaning operations, as a solvent, in organic synthesis, and refrigerants and fumigants (Frear, 1969). The United States production of this compound in 1973 was over 451 million pounds (USITC 1975).

Trichloroethylene is slightly soluble in water (CRC Handbook of Chemistry and Physics, 1970-1971). It can be formed during chlorination of water (EPA, 1975d). The 10-city survey indicated that finished water of five supplies contained trichloroethylene, at 0.1 - 0.5 μg/liter (EPA, 1975a).

II. METABOLISM

Butler (1949) indicated that trichloroacetic acid, trichloroethanol, and small amounts of chloroform and monochloroacetic acid were the metabolic products of trichloroethylene. Ikeda and Ohtsuji (1972) reported that rats excrete 5 - 7 times more trichloroethanol than trichloroacetic acid after exposure to trichloroethylene. The excretion of trichloroethylene and trichloroacetic acid in the urine has been used to some extent to measure trichloroethylene exposure.

III. HEALTH ASPECTS

A. Observations In Man

Exposure to trichloroethylene results in central nervous system depression, incoordination, and unconsciousness, as evidenced by its use as an anesthetic. Acute human exposures have occurred, but have not always been clear cut cases of exposure to a single entity. The report of Feldman *et al.* (1970) concerned a person who was exposed to trichloroethylene vapors from an overheated degreasing unit. He experienced nausea, vomiting, blurred vision, and numbness of the face 10 - 12 h after exposure. The recovery of sensation in the face and motor function of facial muscles occurred slowly over an 18-month period. Sagawa *et al.* (1973) reported accidental exposure of a young woman to vapor and mist of trichloroethylene, which resulted in unconsciousness and a permanent residual disability with respect to mobility. In fatal cases of acute trichloroethylene exposure reported by Kleinfeld and Tabershaw (1954), there was no tissue abnormality at autopsy. Based on chronic exposure of human work populations there are no reported problems with respect to hepatotoxicity. Both Stewart *et al.*

(1970) and Ikeda and Imamura (1973) reported a rather prolonged (2 - 3 days) biologic half-life for trichloroethylene.

The NIOSH (1973) recommended the occupational exposure to trichloroethylene at not in excess of 100 ppm as a time-weighted average exposure for an 8 h workday.

B. Observations in Other Species

Acute effects. The acute oral LD_{50} of trichloroethylene in rats was 4,920 mg/kg (Registry of Toxic Effects of Chem. Substances, 1975). Comparative studies of acute toxicity of halogenated hydrocarbon solvents have also demonstrated that near-lethal doses of trichloroethylene are necessary to produce mild hepatic dysfunction (Klaassen and Plaa, 1966). Baker (1958) reported severe changes in the cerebellum, particularly in the Purkinje cell layers in dogs exposed to 3,000 ppm of trichloroethylene vapor. The dogs were exposed from 2 - 8 h/day for up to 6 days.

Chronic effects. In a study of the chronic effects of trichloroethylene, a 6-month inhalation exposure to 3,000 ppm resulted in increased liver and kidney weights in mice and rats (Adams et al., 1951).

Mutagenicity. No available data.

Teratogenicity. Schwetz et al. (1975) described the acute exposure of mice and rats to 300 ppm, 7 h/day, on days 6 - 15 of gestation. No embryonal or fetal toxicity was noted, nor were there any teratogenic effects.

Carcinogenicity. Trichloroethylene was tested (for carcinogenicity by NCI (1976) in a chronic feeding study. Both sexes of Osborne-Mendel rats and $B6C3F_1$ mice were used. Animals were exposed to two doses (MTD and 1/2 MTD) by oral gavage 5 times/week for 78 weeks. All animals were then kept until terminal sacrifice at 110 weeks. The doses used were as follows: 1097 and 549 mg/kg for both male and female rats and 2,339 and 1,169 mg/kg for male mice and 1,739 and 869 mg/kg for female mice. Significant dose related hepatocellular carcinoma was seen in both male and female mice, but the rats were quite resistant to the carcinogenic effects of trichloroethylene.

IV. CARCINOGENIC RISK ESTIMATES

The statistical assessment of human cancer risk associated with trichloroethylene in drinking water is based on the results of a carcinogenesis bioassay experiment with animals (NCI, 1976). Trichloroethylene was dissolved in corn oil and administered by gavage to male and female B6C3F$_1$ mice 5 days/week for 78 weeks. The surviving mice were sacrificed at 90 weeks, and a complete necropsy and microscopic evaluation of all animals were conducted. Highly significant differences in the incidence of hepatocellular carcinomas were found between treated and control mice of both sexes.

The available sets of dose response data were individually considered as described in the risk section in the chapter on margin of safety. Each set of dose response data was used to statistically estimate both the lifetime risk and an upper 95% confidence bound on the lifetime risk at the low dose level. These estimates are of lifetime human risks and have been corrected for species conversion on a dose/surface area basis. The risk estimates are expressed as a probability of cancer after a lifetime consumption of 1 liter of water/day containing Q ppb of the compound of interest. For example, a risk of 1×10^{-6} Q implies a lifetime probability of 2×10^{-5} of cancer if 2 liters/day were consumed and the concentration of the carcinogen was 10 ppb (i.e., Q=10). This means that at a concentration of 10 ppb during a lifetime of exposure this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the United States is taken to be 220 million people this translates into 4,400 excess lifetime deaths from cancer or 62.8/year. Since several data sets are typically available the range of the low-dose risk estimates are reported. For trichloroethylene at a concentration of 1 μg/liter (Q=1) the estimated risk for man would be 1.1 - 36 X 10^{-7} Q. The upper 95% confidence estimate of risk at the same concentration is 1.6 - 93 X 10^{-7} Q.

It should be emphasized that these extrapolations are based on a number of unverifiable assumptions: extrapolation from high exposure to low exposure in mice, on the basis of a multistage mathematical model; extrapolation from mouse to man, on the basis of the surface-area rule; and extrapolation from gavage exposure to oral exposure assumed equal. These estimated human risks should be taken as crude estimates at best.

IV. CONCLUSIONS AND RECOMMENDATIONS

It is concluded that trichloroethylene has low toxicity, both acute and chronic. Only after high acute accidental exposures have effects been reported in humans. These have been related to the depressant effect on the central nervous system. No fetal toxicity or teratogenic effects have been reported. Carcinogenic bioassay demonstrated hepatocellular carcinoma in one strain of mice. The chronic toxicity data are summarized in Table VI-58.

TABLE VI-58. Summary of Chronic Toxicity Data for Trichloroethylene

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse-effect Level or Lowest Minimal-effect Level	Effect Measured	Reference
Mouse (male)	78 wks.	0, 1169, 2339 mg/kg/day, gavage 20-50 animals/group	1169 mg/kg/day	Hepatomas	NCI, 1976
Mouse	78 wks.	0, 869, 1739 mg/kg/day, gavage 20-50 animals/group	869 mg/kg/day	Hepatomas	NCI, 1976

[This compound is an animal carcinogen]

TRICHLOROFLUOROMETHANE

I. INTRODUCTION

Trichlorofluoromethane (Freon 11) is used in the manufacture of aerosol sprays, refrigerants, blowing agents, and cleaning compounds and in fire extinguishers (EPA, 1975d). The United States production of this compound in 1973 was over 333 million pounds (USITC, 1975). It has been reported that the finished water of Washington, D.C., contained less than 1 µg/liter of trichlorofluoromethane (Scheiman et al., 1974).

II. METABOLISM

When trichlorofluoromethane was inhaled by humans, recovery of the intact compound in exhaled air was 79 - 99% and in urine, 0.07 - 0.09%, and metabolites amounted to 0.2% or less (Mergner et al., 1975). Terrill (1974) demonstrated that absorption of a fluorocarbon, F115, in dogs was 35 - 48 times greater by inhalation than by oral administration. Charlesworth (1975) indicated that the main factor affecting the fate of fluorocarbons is the body fat, where they are concentrated and slowly released into the blood at concentrations that should not cause any risk of cardiac sensitization. Blake and Mergner (1974) showed that inhalation of ^{14}C labeled Freon 11 by dogs resulted in complete recovery in exhaled air (101.8%) in 1 h, and recovery from urine of only .0095%, and no evidence of biotransformation. However, Niazi and Chiou (1975), who administered Freon 11 intravenously in dogs, demonstrated that, although the compound is rapidly eliminated from the bloodstream, it is then eliminated via three compartments with half-lives of 3.2, 16, and 93 m.

III. HEALTH ASPECTS

A. Observations In Man

By inhalation, large, acute doses have resulted in cardiac sensitization (arrhythmia) or bronchial constriction leading to death (Dollery et al., 1970). The threshold limit value (ACGIH, 1967) is 1,000 ppm, or 5,600 mg/m³.

B. Observations In Other Species

Acute effects. Slater (1965) gave a single oral dose of 2.5 g/kg to rats and reported no liver pathology. Lester and Greenberg (1950) reported that inhalation by rats of aerosol containing 6% Freon 11 resulted in loss of postural reflex, 8% resulted in loss of righting reflex, 9% resulted in unconsciousness, and 10% was lethal. Mice that inhaled 10%

developed cardiac arrhythmia (Aviado and Belej, 1975); dogs that inhaled 2.5% had decreased myocardial function, including cardiac output (Aviado and Belej, 1975); and monkeys that inhaled 5% developed tachycardia and hypotension (Belej and Aviado, 1973).

Chronic effects. Kudo *et al.* (1971) reported that mice given oral doses of 15, 55, and 220 mg/kg/day for a month showed only slight effects on food utilization.

Mutagenicity. No available data.

Carcinogenicity. In a study by Epstein *et al.* (1967) mice given 0.1 ml of 10% solution solution at 1 and 7 days of age and 0.2 ml at 14 and 21 days of age were observed for a year. No evidence of a carcinogenic effect of Freon 11 was found.

Teratogenicity. Paulet *et al.* (1974) reported that inhalation at 200,000 ppm of a 9:1 mixture of Freon 12 and Freon 11 by rats on days 4 - 16 of gestation and rabbits on days 5 - 20 of gestation did not induce any embryotoxic or teratogenic effects.

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, and long term oral toxicity of trichlorofluoromethane, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before limits in drinking water can be established.

VINYL CHLORIDE

I. INTRODUCTION

Vinyl chloride (chloroethene) monomer is not known to occur in nature. It is commercially synthesized by the halogenation of ethylene. In the United States, the vinyl chloride monomer is used primarily in the production of polyvinyl chloride resins for the building and construction industries. Because it has been confirmed that vinyl chloride monomer is a human and animal carcinogen, the sale of propellents and all aerosols containing it was banned in 1974 (EPA, 1974; United States Consumer Product Safety Commission, 1974). The occupational standard for atmospheric vinyl chloride in the United States is 1 ppm (2.56 mg/m^3) or less for 8 h/day and 5 days/week. The United States production of vinyl chloride in 1975 was 5.35 billion pounds (USITC, 1975).

Vinyl chloride monomer is slightly soluble in water (<0.11% by weight at 25°C) (CRC Handbook of Chemistry and Physics, 1970-1971). Results of the 10-city survey (EPA, 1975a) indicate that vinyl chloride was present in the finished water of Miami, at 5.6 µg/liter, and Philadelphia, at 0.27 µg/liter.

II. METABOLISM

After inhalation of ^{14}C-vinyl chloride by rats, 2 - 12% of the (10- or 1,000-ppm ppm) dose was eliminated as vinyl chloride in the expired air within 72 h. The 10-ppm exposure produced the higher urinary excretion and lower expired amount. Pulmonary excretion was fast and followed first-order kinetics, but the slower urinary excretion of vinyl chloride metabolites followed a biphasic elimination pattern. Three urinary metabolites have been detected: N-acetyl-S-(2-hydroxyethyl)cysteine, thiodiglycolic acid, and an unidentified substance (McGowan et al., 1975).

Oral doses of 0.05 - 1.0 mg/kg in rats yielded similar information. The pulmonary excretion was monophasic at these doses, and the urinary metabolites are the same. At an oral dose of 100 mg/kg, the pulmonary excretion is biphasic and a greater percentage of the administered dose is expired as vinyl chloride--67%, compared with 1 or 2% at the lower dose.

The above data all indicate a dose-dependent fate of vinyl chloride after inhalation or oral administration in rats. The primary mechanism of detoxification of vinyl chloride or its reactive metabolites involves conjugation with hepatic glutathione. The glutathione conjugates are then subject to hydrolysis, yielding the cysteine conjugates found in the urine. This is consistent with the observed decrease in hepatic nonprotein sulfhydryl groups in rats exposed to vinyl chloride (Hefner *et al.*, 1975).

III. HEALTH ASPECTS

A. Observations in Man

In studies of the acute effects of vinyl chloride in man, it has been shown to produce central nervous system dysfunction, sympathetic-sensory polyneuritis, and organic disorders of the brain (Smirnova and Granik, 1970). In a series of studies on workers in the polyvinyl chloride industry, scleroma-like skin alterations, Raynaud's syndrome, and acroosteolysis were observed (Juehe and Lange, 1972; Juehe *et al.*, 1974; Berk *et al.*, 1975; Marsteller *et al.*, 1975).

To date, 48 cases of hepatic angiosarcoma have been diagnosed in industrial vinyl chloride workers around the world. All authenticated cases were found in workers engaged in closed-in plants handling very large quantities of liquefied vinyl chloride under pressure (Anon., 1974; Makk *et al.*, 1976). Exposure concentrations were high, probably ranging from 1,000 ppm to several thousands ppm.

Lesions of the skin, bones, liver, spleen, and lungs have also been reported after chronic exposure to the compound (Popper and Thomas, 1975; Gedigk *et al.*, 1975; Thomas and Popper, 1975.

B. Observations in Other Species

Acute effects. Because of the physical properties of vinyl chloride, the effects of oral exposure to it have not been examined. With respect to inhalation toxicity, vinyl chloride has been shown to produce lung congestion and some hemorrhaging, blood-clotting difficulties, and congestion of liver and kidneys in laboratory animals (Mastromatteo *et al.*, 1960). After 2 h at 5% vinyl chloride, rats showed moderate intoxication; 2 h at 15% provoked respiratory failure (Lester *et al.*, 1963).

Mutagenicity. In a study by Malaveille *et al.* (1975), exposure of *Salmonella typhimurium* strains TA1530, TA1535, and G-46 to vinyl chloride increased the number of his +revertants/plate 16, 12 or 5 times over the spontaneous mutation rate. The mutagenic response for TA1530 strain was increased when S-9 liver fractions from humans, rats, or mice were added. Exposure of *S. typhimurium* to vinyl chloride gas produced no mutagenic effect without microsomal activation (Rannug *et al.*, 1974).

Carcinogenicity. In a study to determine the carcinogenic effects of vinyl chloride inhalation, Viola (1970a,b) and Viola *et al*., (1971) reported that 30,000 ppm, 4 h/day, 5 days/week, for 12 months produced tumors of lungs, skin, and bones in Wistar rats. Along the same lines, 250-10,000 ppm, 4 h/day, 5 days/week, for 12 months was reported by Maltoni and Lefemine (1974a,b) to increase the incidence of cancer in rats. Zymbal gland carcinoma, angiosarcoma, and nephroblastoma were most prominent. Latency for the development of these cancers ranged from 59 to 83 weeks. In another study, in which lower concentrations (50 ppm) were used, a marked change in the latency for finding tumors indicated the possibility of a threshold for induction (Maltoni and Lefemine, 1975).

Teratogenicity. Vinyl chloride, was administered for 7 h/day on days 6 - 18 of gestation in mice, rats, and rabbits. It was concluded that, although maternal toxicity was observed, vinyl chloride alone did not cause significant embryonal or fetal toxicity and was not teratogenic in any of the species at the concentrations tested (John *et al*., 1975).

IV. CARCINOGENIC RISK ESTIMATES

In a recent study by Maltoni *et al*. (1975), rats were given vinyl chloride in olive oil by gavage four or five times per week for 52 weeks and held for their life span. The available set of dose response data was considered as described in the risk section in the chapter on margin of safety. Each set of dose response data was used to statistically estimate both the lifetime risk and an upper 95% confidence bound on the lifetime risk at the low dose level. These estimates are of lifetime human risks and have been corrected for species conversion on a dose/surface area basis. The risk estimates are expressed as a probability of cancer after a lifetime consumption of 1 liter of water per day containing Q ppb of the compound of interest. For example a risk of $1x10^{-6}$ Q implies a lifetime probability of $2x10^{-5}$ of cancer if 2 liters/day were consumed and the concentraton of the carcinogen was 10 ppb (i.e., Q=10). This means that at a concentration of 10 ppb during a lifetime exposure this compound would be expected to produce one excess case of cancer for every 50,000 persons exposed. If the population of the United States is taken to be 220 million people this translates into 4,400 excess lifetime deaths from cancer or 62.8/year. For vinyl chloride a concentration of 1 µg/liter (Q=1) the estimated risk for man is $3.0x10^{-7}$ Q. The upper 95% confidence estimate at the same concentration is $6.1x10^{-7}$ Q.

IV. CONCLUSIONS AND RECOMMENDATIONS

Vinyl chloride has acute and chronic toxic effects in animals and man. In addition to its chronic toxicity, it has been clearly shown to be a carcinogen in animals and man, with dose- and time-related properties, and to be a mutagen in *in vitro* systems. Its carcinogenic property has been demonstrated by oral administration. This route is more effective (efficient) in producing the characteristic tumor, angiosarcoma, than is loading the atmosphere with similar amounts of vapor. In animal studies, vinyl chloride has induced a wide variety of tumors, in addition to the characteristic and otherwise rare angiosarcoma. The available chronic toxicity data are summarized in Table VI-59.

TABLE VI-59. Summary of Chronic Toxicity Data for Vinyl Chloride

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse effect Level or Lowest Minimal-effect Level	Effect Measured	Reference
Rat	12 mos.		30,000 ppm, 4h/day, 5 day/wk	Tumors of skin and bones	Viola, 1970a,b; Viola et al., 1971
Rat	12 mos.	0,3.33,16.65, 50 mg/kg/day	16.65 mg/kg/day (gavage)	Angiosarcomas	Maltoni et al., 1975

(This compound is an animal and human carcinogen.)

XYLENES

I. INTRODUCTION

Xylene (dimethylbenzene) is formed in petroleum, coal tar, and coal gas distillation. It is used in aviation gasolines, in rubber cements, in the manufacture of solvents and protective coatings, and in the synthesis of organic chemicals (EPA, 1975d). The United States production of xylene in 1973 was over 5.94 billion pounds (USITC, 1975). Xylene is insoluble in water (CRC Handbook of Chem. & Phys., 1970-1971). The finished water of the New Orleans area (EPA, 1975c) contained xylene at 4.1 µg/liter.

II. METABOLISM

Oxidation of xylene to phenolic metabolites has been reported by a number of investigators, including Bakke and Scheline (1970). A dosage of 100 mg/kg in rats gave the following results: *o*-xylene metabolized to 3,4-dimethylphenol (0.1% of dose) and 2,3 dimethylphenol (0.03% of dose); *m*-xylene metabolized to 2,4-methylphenol (0.9% of dose); *p*-xylene metabolized to 2,5-dimethylphenol (1.0% of dose). 2-Methylbenzyl alcohol was also reported as a metabolite of *o*-xylene. In man, Ogata *et al.* (1970) reported that 72% of absorbed *m*-xylene was excreted as *m*-methylhippuric acid within 18 h.

III. HEALTH ASPECTS

A. Observations In Man

Carpenter *et al.* (1975) exposed human volunteers to xylene at 460, 1,000, and 2,000 mg/m^3 (approximately 100, 225, and 450 ppm) for 15 m. All volunteers detected the odor, and several reported olfactory fatigue and eye irritation at the higher concentrations. Morley *et al.* (1970) reported an exposure of three painters to xylene at an estimated 10,000 ppm. Two of the three were in this atmosphere for approximately 18 h. One died, with evidence of severe lung congestion and intra-alveolar hemorrhage; the two survivors experienced confusion for some time after recovery, had impairment of renal function with recovery at approximately 2 weeks, and may also have had minimal liver damage.

The NIOSH (1975) recommended a time-weighted average exposure not to exceed 100 ppm of xylene for a 10 h workday, 40 h workweek.

6. Observations in Other Species

Acute effects. The acute oral LD_{50} in rats, as reported by Wolf et al. (1956), was 4.3 g/kg. Inhalation studies reported by Lazarov (1929) indicated lethal effects in mice exposed to o-xylene at 30 mg/liter (6,900 ppm), m-xylene at 50 mg/liter (11,500 ppm, or p-xylene at 15 - 35 mg/liter (3,450 - 8,050 ppm). Cameron et al. (1938) reported some deaths in mice exposed to the various isomers at 2,000 - 4,000 ppm. Hine and Zuidema (1970) reported the xylenes to be moderately irritating to the skin of animals. Batchelor (1927) exposed rats to xylene vapor for 18 - 20 h/day. At 1,600 ppm, two of four rats died within 4 days. Initial signs were incoordination and irritation of the mucous membranes. The white-cell count was decreased after 4 days of exposure. Four rats exposed to 980 ppm for 7 days had hyperplastic bone marrow and spleen, with kidney congestion. One animal had a 12% reduction in white cells. One of eight rats exposed to 620 ppm for 7 days had a 30% reduction in white-cell count.

Subchronic and chronic effects. Smyth and Smyth (1928) exposed guinea pigs to xylene at 300 ppm for 4 h/day, 6 days/week for 2 months. Slight liver and lung effects were reported at necropsy. Speck and Moeschlin (1968) found no adverse effects on the hematopoietic system after subcutaneous administration at 300 mg/kg/day for 6 weeks or 700 mg/kg/day for 9 weeks. The authors suggested that other reports of myelotoxicity of xylene are probably related to benzene contamination. Fabre (1960) reported that rabbits exposed to benzene-free xylene (at 5 mg/liter, or 1,150 ppm) for 40 - 55 days had decreased red- and white-cell counts. Carpenter et al. (1975) exposed rats and dogs to p-xylene at 805, 460, or 175 ppm (3.5, 2.0, or 0.77 mg/liter) for 6 h/day, 5 days/week, for 13 weeks. No gross or microscopic lesions were reported, and all hematologic characteristics were comparable with those of control rats.

Mutagenicity. No available data.

Carcinogenicity. No available data.

Teratogenicity. Xylene has been reported to produce developmental defects in chicken embryos (Kucera, 1968).

IV. CONCLUSIONS AND RECOMMENDATIONS

In view of the relative paucity of data on the mutagenicity, carcinogenicity, teratogenicity, and long term oral toxicity of Xylene, estimates of the effects of chronic oral exposure at low levels cannot be made with any confidence. It is recommended that studies to produce such information be conducted before final limits in drinking water can be established.

D. SUMMARY

The organic contaminants identified in drinking water make up a small fraction of the total organic matter present. Although approximately 90% of the volatile organics in drinking water have been identified and quantified, these represent no more than 10% of the total organic material. Only 5 - 10% of the non-volatile organic compounds, which comprise the remaining 90% of the total organic material in water have been identified.

Considered were 74 non-pesticide organic compounds of the approximately 309 volatile organic compounds so far identified in drinking water, and 55 pesticides. Some of the pesticides studied have not yet been detected in drinking water, but were included because they are or have been used in large quantities. A compound was selected for consideration if any of the following criteria applied:

1. Experimental evidence of toxicity in man or animals including carcinogenicity, mutagenicity, teratogenicity.
2. Identified in drinking water at relatively high concentrations.
3. Molecular structure closely related to that of another compound of known toxicity.
4. Pesticide in heavy use which could result in contamination of drinking water supplies.
5. Listed in the Safe Drinking Water Act or National Interim Primary Drinking Water Regulations.

Toxicological information about the compounds of interest was variable in quality and quantity and in some instances, inadequate for a proper assessment of toxicity. Although the carcinogenic effect of these compounds was of primary concern, evidence for other toxic effects on target organ systems was also considered. Sufficient data were available for less than one-fourth of the non-pesticide organic compounds and three-fourths of the organic pesticides investigated to permit judgement as to either the carcinogenicity of the compound or the establishment of an Acceptable Daily Intake (ADI).*

The ADI represents an empirically derived value that reflects a particular combination of both knowledge and uncertainty concerning the relative safety of a chemical. When there is more confidence about data derived from animal experiments or observations on humans the uncertainty factor is smaller than when little is known about the potential toxicity of a chemical. These numbers are not meant to represent a guaranteed safety level, but rather to indicate a level at which exposure to the single chemical in question is not anticipated to produce an observable toxic response in man. The ADI values do not consider interactions (e.g. synergism, antagonism) among the many possible contaminants. Furthermore the ADI numbers do not represent a safe level in drinking water, because they do not take into account what fraction of the potential contaminant intake may come from water.

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*The Committee considered several alternative terms, other than ADI, but concluded that the introduction of a substitute for ADI might well lead to confusion. The term "Acceptable Daily Intake" is used throuhout the discussion because of its adoption by international organizations.

Suggested no-adverse health effects concentrations in water have been calculated based on two sets of assumptions; (1) that 20% of total intake of a material is from water and 80% from other sources, and (2) that 1% of total intake is from water and 99% from other sources (See Table VI-61). Similar calculations can be made for other materials discussed in this report using such data as may be available with regard to concentration of the contaminant in food or other sources.

Because of the lack of consistency in the experimental data on the effects of many substances, "no-adverse-health-effect" levels cannot be firmly specified for all organic contaminants. Most of the materials considered have not been studied sufficiently to firmly establish their carcinogenic potential. Interactions such as additive toxicity, synergism, and antagonism have not been considered in development of risk assessments. What ultimately may be most important is the interaction of these compounds with each other and with other material in contributing to the total body burden resulting from multiple sources of contaminant exposure. For these reasons the ADI is intended to be used only as a guide for assessment of toxicity from chronic exposure. Furthermore, an ADI is not meant to provide a basis for the continuing discharge of a compound into the environment.

In the present limited state of our knowledge concerning structure-activity relationships for carcinogenic and other toxic effects, one cannot consistently and accurately extrapolate these properties from one compound to another. Nevertheless, in certain specific instances (for example, the substitution of bromine for chlorine in a halogenated methane) it is presumed that the relationship is sufficiently strong to justify the suspicion that the related compounds may be similarly toxic.

The potential for existing concentrations of organic pesticides and other organic contaminants in drinking water to adversely affect health, cannot be answered with certainty at this time. The key issue is whether or not certain organic chemicals found in very low concentrations can cause or increase the rate of cancer development in man. Even though several of these chemicals have demonstrated carcinogenicity in laboratory animals, the extrapolation of such results to man remains difficult for a number of reasons.

Because the bioassays that have been used to establish carcinogenicity of certain organic chemicals are conducted at doses which are hundreds to thousands of times greater than the levels at which these chemicals occur in water, the risks at these low levels must be obtained by extrapolation from higher doses. There is no hard evidence that low level oral exposure to any of these chemicals produces cancer. An argument has been made that the dose levels used to establish carcinogenicity are so high that they overwhelm normal detoxification and/or repair mechanisms and produce cancer by some mechanism which does not occur under low-dose conditions. Experimental animals subjected to such high doses could be considered a population different from those exposed to lower doses which do not produce pathological alterations and changes in pharmacokinetic parameters, or biochemistry.

Extrapolating from laboratory animals to man would be more meaningful if comparative metabolic information between the different species were available. Some species do not metabolize a parent compound to its activated form so that use of these species in toxicological bioassays is inappropriate if the compound undergoes activation in man. The converse situation also is true. Differences may also occur with respect to other parameters such as rates of biotransformation, absorption, excretion, and biological half life.

Risk assessments based on extrapolations which fail to consider species differences with respect to sensitivity, tissue susceptibility, kinetics, pathology or biotransformation pathways may be inappropriate. This kind of information is not presently available.

In light of such uncertainties, a cautious approach must be adopted when dealing with potentially harmful chemicals. Even more uncertainty exists when one considers the possibility that some of these chemicals may also be mutagenic or teratogenic. The methodologies used to establish these effects are even less applicable to man than cancer bioassays.

For many of the organic compounds identified in drinking water, virtually no toxicity data are available. Ideally, all of these agents (as well as any new ones) should be subjected to an extensive battery of toxicity tests including chronic bioassay. In practice, there is a need to determine those agents for which the generation of data is most pressing.

The main factors identified in the assignment of priorities are:

1. The relative concentrations of the compounds and the number of people likely to be exposed as well as the identity of defined subpopulations exposed.
2. The number of water systems in which they occur.
3. Positive responses to *in vitro* mutagenic screening systems.
4. Positive responses to *in vitro* carcinogen pre-screens (mammalian cell transformations).
5. Similarity of chemical structure of the test compound to those of other compounds having defined toxic properties (i.e. structure-activity relationships).
6. Relationship of dose from water to total body burden.

A number of assays using bacteria and yeast have shown promise in yielding high correlations between mutagenic activity and known carcinogenic activity for certain classes of materials. These may prove to be useful in establishing a first level screen for potential carcinogens.

CONCLUSIONS

Carcinogenicity

Table VI-60 lists those specific organic contaminants for which positive data on carcinogenesis exist. For these compounds, where adequate (lifetime) feeding studies were available, a statistical extrapolation of risk was performed. The statistical methodology is described in detail in the chapter on Margin of Safety and Extrapolation. The numbers in Table VI-60 are upper 95% confidence estimates of cancer risk to man from a lifetime of exposure to a particular compound. These estimates have been corrected (animal dose to human dose) on a dose/surface area basis.

TABLE VI-60

Categories of Known or Suspected Organic Chemical Carcinogens Found in Drinking Water

Compound	Highest Observed Concentrations in Finished Water (µg/l)	Upper 95% Confidence Estimate of Lifetime Cancer Risk per µg/liter*
Human Carcinogen*		
Vinyl Chloride **	10	5.1×10^{-7}
Suspected Human Carcinogens		
Benzene	10	I.D.**
Benzo(a)pyrene**	D.	I.D.
Animal Carcinogens		
Dieldrin	8	2.6×10^{-4}
Kepone	N.D.	4.4×10^{-7}
Heptachlor	D.	4.2×10^{-5}
Chlordane	0.1	1.8×10^{-5}
DDT/DDE	D.	1.2×10^{-5}
Lindane (γ-BHC)	0.01	9.3×10^{-6}
α-BHC	D.	6.5×10^{-6}
β-BHC	D.	4.2×10^{-6}
PCB (Aroclor 1260)	3	3.1×10^{-6}
ETU	N.D.	2.2×10^{-4}
Chloroform	366	3.7×10^{-7}
Carbontetrachloride	5	1.5×10^{-7}
PCNB	N.D.	1.4×10^{-7}
Trichloroethylene	0.5	1.3×10^{-7}
Diphenylhydrazine	1	I.D.
Aldrin	D.	I.D.
Suspected Animal Carcinogens		
Bis(2-chloroethyl)ether	0.42	1.2×10^{-6}
Endrin	0.08	I.D.
Heptachlor epoxide	D.	I.D.

**I.D. = Insufficient data to permit a statistical extrapolation of risk.

N.D. = Not detected

D. = Detected but not quantified

* = See text for details (Introduction and Chap. II)

** = also an animal carcinogen

aHuman Carcinogen - Based on strong epidemiological evidence and toxicological studies in animals.

Suspected Human Carcinogen - Based on limited epidemiological evidence in man and equivocal toxicologicl studies in animals.

Animal Carcinogen - Based on toxicological studies in at least one species of animal.

Suspected Animal Carcinogens - Based on equivocal toxicological studies in animals or on a structural similarity to a known carcinogen.

Bacterial Mutagenicity

In addition to examining data from animal feeding studies for the identification of suspect carcinogens, data for mutagenesis in bacteria, or other test systems were also examined. Available data are summarized as follows:

1. Benzo(a)pyrene, chlorodibromomethane, captan, and Folpet have been found to be mutagenic.
2. Bromoform and vinyl chloride, weakly mutagenic.
3. Carbon tetrachloride, bromobenzene, nicotine, DDE, dieldrin, carbaryl and trifluraline, non-mutagenic.

Teratogenicity

Data on teratogenic potential exist for 22 of the compounds under study. Hexachlorophene, nicotine, the phthalate esters, 2,4-D, 2,4,5-T, and Folpet have been shown to be teratogens, while benzene, benzo(a)pyrene, carbon tetrachloride, PCB's, Captan, Carbaryl, Chlordan, DDT, Kepone, Malathion, Methylparathion, Mirex, Paraquat, PCNB and Parathion have been reported to be non-teratogenic. Nowhere is the paucity of toxicologic data more evident than in the data on teratogenesis.

Non-Carcinogenic Toxicity

For 46 compounds there were sufficient data to calculate ADI's. These are summarized in Table VI-61. Occasionally an ADI was calculated when less than lifetime exposure studies were available. The selection of responses by which toxicity was measured was variable.

For 29 organic contaminants and pesticides there were insufficient data to calculate ADI's. The available toxicological data are included in the text and the compounds are listed in Table VI-62. Even a superficial evaluation could not be done on 32 compounds due to inadequacy of toxicological data. These compounds are listed in Table VI-63, together with their reported occurences in drinking waters of the United States.

TABLE VI-61

Organic Pesticides and Other Organic Contaminants in Drinking Water, Concentration, Toxicity, ADI and Suggested No-Adverse Effect Levels

Compound	Maximum Observed Concentrations in H_2O, µg/l	Maximum Dose Producing No Observed Adverse Effect mg/kg/day	Uncertainty Factor†	ADI** mg/kg/day	Suggested No-Adverse Effect Level from H_2O, µg/l Assumptions* 1	2
2,4-D	0.04	12.5	1,000	0.0125	87.5	4.4
2,4,5-T		10.0	100	0.1	700	35.0
TCDD		10^{-5}	100	10^{-7}	$7x10^{-4}$	$3.5x10^{-5}$
2,4,5-TP	detected**	0.75	1,000	0.00075	5.25	0.26
MCPA		1.25	1,000	0.00125	8.75	0.44
Amiben		250	1,000	0.25	1750.0	87.5
Dicamba		1.25	1,000	0.001125	8.75	0.44
Alachlor	2.9	100	1,000	0.1	700.0	35.0
Butachlor	0.06	10	1,000	0.01	70.0	3.5
Propachlor		100	1,000	0.1	700.0	35.0
Propanil		20	1,000	0.02	140.0	7.0
Aldicarb		0.1	100	0.001	7	0.35
Bromacil		12.5	1,000	0.0125	87.5	4.4
Paraquat		8.5	1,000	0.0085	59.5	2.98
Trifluralin (also for Nitralin and Benefin)	detected	10	100	0.1	700.0	35.0
Methoxychlor		10	100	0.1	700.0	35.0
Toxaphene		1.25	1,000	0.00125	8.75	0.44
Azinphosmethyl		0.125	10	0.0125	87.5	4.4
Diazinon		0.02	10	0.002	14.0	0.7
Phorate (also for Disulfoton)		0.01	100	0.0001	0.7	0.035

TABLE VI-51 (continued)

Organic Pesticides and Other Organic Contaminants in Drinking Water, Concentration, Toxicity, ADI and Suggested No-Adverse Effect Levels

Compound	Maximum Observed Concentrations in H_2O, ug/l	Maximum Dose Producing No Observed Adverse Effect mg/kg/day	Uncertainty Factor*	ADI** mg/kg/day	Suggested No-Adverse Effect Level, From H_2O, ug/l Assumption* 1	2
Carbaryl		8.2	100	0.082	574	28.7
Ziram (and Ferbam)		12.5	1,000	0.0125	87.5	
Captan		50	1,000	0.05	350	17.5
Folpet		160	1,000	0.16	1120	56.0
Hexachlorobenzene	6.0	1	1,000	0.001	7	0.35
Paradichlorobenzene (also orthodichlorobenzene)	1.0	13.4	1,000	0.0134	93.8	4.7
Parathion (and Methyl parathion)		0.043	10	0.0043	30	1.5
Malathion		0.2	10	0.02	140	7.0
Maneb (and Zineb and Dithane)		5.0	1,000	0.005	35	1.75
Thiram		5.0	1,000	0.005	35	1.75
Atrazine	5.0	21.5	1,000	0.0215	150	7.5
Propazine	detected	46.4	1,000	0.0464	325	16.2
Simazine	detected	215.0	1,000	0.215	1505	75.25

TABLE VI-61 (continued)

Organic Pesticides and Other Organic Contaminants in Drinking Water: Concentration, Toxicity, ADI and Suggested No-Adverse Effect Levels

Compound	Maximum Observed Concentrations in H_2O, µg/l	Maximum Dose Producing No Observed Adverse Effect mg/kg/day	Uncertainty Factor*	ADI** mg/kg/day	Suggested No-Adverse Effect Level From H_2O, µg/l Assumptions*** 1	2
di-n-butyl phthalate	5.0	110	1,000	0.11	770	38.5
di (2-ethyl hexyl) phthalate	30.0	60	100	0.6	4,200	210.0
hexachlorophene	0.01	1	1,000	0.001	7	0.35
methyl methacrylate	1.0	100	1,000	0.1	700	35.0
pentachlorophenol	1.4	3	1,000	0.003	21	1.05
styrene	1.0	133	1,000	0.133	931	46.5

* Uncertainty Factor - the factor of 10 was used where good chronic human exposure data was available and supported by chronic oral toxicity data in other species, the factor of 100 was used where good chronic oral toxicity data were available in some animal species, and the factor of 1000 was used with limited chronic toxicity data or when the only data available were from inhalation studies.

** Acceptable Daily Intake (ADI) - Maximum dose producing no-observed adverse effect divided by the Uncertainty Factor

*** Assumptions: Average weight of human adult = 70 kg. Average daily intake of water for man = 2 liters.

1. 20% of total ADI assigned to water

   80% from other sources

2. 1% of total ADI assigned to water

   99% from other sources

**detected but not quantified

TABLE VI-62

Organic Pesticides and Other Organic Contaminants Found in Drinking Water, With Insufficient Data on Chronic Toxicity To Calculate an ADI

	Highest Concentration in Finished Water, µg/l
Acetaldehyde	0.1
Acrolein*	
Bromobenzene	detected
Bromoform	detected
Carbon disulfide	detected
Chloral	5.0
Chlorobenzene	5.6
Cyanogen chloride	0.1
1,2-Dichloroethane	21.0
2,4-Dichlorophenol	36.0
2,4-Dimethylphenol	detected
e-Caprolactam	detected
Hexachloroethane	4.4
O-Methoxyphenol	detected
Methyl chloride	detected
Methylene chloride	7.0

Phenylacetic acid	8.0
Phthalic anhydride	detected
Propylbenzene	<5.0
t-Butyl alcohol	0.01
Tetrachloroethane	8.0
Tetrachloroethylene	<5.0
Toluene	11.0
Trichlorobenzene	1.0
1,1,2-Trichloroethane	detected
Nicotine	3.0
Methomyl*	
Cyanazine	detected
Xylene	<5.0

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detected = detected but not quantified
*not detected in finished water

TABLE VI-63

Organic Contaminants Found in Drinking Water With No Available Information On Chronic Toxicity

Compound	Highest Concentration in Finished Water, µg/l	Highest Concentration in Raw Water, µg/l
1,2-Bis (chloroethoxy)ethane	0.03	
Bis(2-chloroisopropyl)ether	1.58	
Bromochlorobenzene	detected	
Bromodichloromethane	116	11
Butyl bromide	detected	
Chloroethyl methyl ether	detected	
Chlorodibromomethane	100	1.4
Chlorohydroxybenzophenone	detected	
Chloromethyl ethyl ether	detected	
Chloropropene	detected	
Crotonaldehyde	5.0	
Dibromobenzene	detected	
Dibromodichloroethane	0.63	
1,3-Dichlorobenzene	<1.0	
Dichlorodifluoroethane	detected	
Dichloroiodomethane	0.5	
1,1-Dichloro-2-hexanone	1.0	
1,2-Dichloropropane	<1.0	
1,3-Dichloropropene	<1.0	
1,2-Dimethoxybenzene	detected	
4,6-Dinitro-2-aminophenol	detected	
Dioctyladipate	20.0	
Hexachloro-1,3-butadiene	0.07	
Isodecane	5.0	
Metachloronitrobenzene	detected	
Methylstearate	detected	
Nonane	4.0	
Octyl chloride	detected	
Pentachlorophenyl methyl ether	0.1	
1,1,3,3-Tetrachloroacetone	1.0	1.0
2,4,6-Trichlorophenol	detected	
Trimethylbenzene	6.1	

RESEARCH RECOMMENDATIONS

1. Because great uncertainty exists in connection with extrapolation of data from the present cancer bioassays, better premises and methodologies are needed to establish the extent to which humans are at risk from the low level exposures to organic substances in water. There is a need to know the extent to which low level exposure to a presumed carcinogen does in fact increase the probability of cancer during the lifetime of an individual.

It is recommended that work be done to better characterize current animal models and also develop new ones. Studies on the comparative metabolism between laboratory animals and man are urgently needed. It is necessary to know, for example, if a laboratory animal metabolizes a test compound in the same manner and rate as man. Better mutagenicity bioassays using mammalian cells should be developed. More work is needed in the area of interactions and synergism which these assay systems could more easily accommodate.

2. Organic material in water is thought by many to be responsible for contributing the initial reactants for many potentially harmful contaminants. To this end total organic carbon (TOC) in drinking water supplies must be better characterized and more extensively determined. Because many halogenated compounds are formed by chlorination of naturally occurring organic substances research on methods for destruction or removal of organic precursors of halogenated compounds prior to chlorination would lead to reduction in chlorinated products and their accompanying health hazards.

3. Epidemiologic studies to obtain quantitative measures of association between the frequency of malignant disease in humans and exposure to specific organic compounds found in drinking water are needed. In particular, ways are needed to develop useful epidemiologic data from examination of small populations of individuals occupationally exposed to drinking water contaminants. A major effort now needs to be directed at determining the health status of workers in industries where there is occupational exposure to compounds identified as animal carcinogens.

More accurate record keeping, a national death index, and more reliable analytical methods to monitor environmental exposure are needed.

4. There is a need for more and better toxicological data, on compounds which could not be evaluated at this time, especially creosote, methyl parathion, and acrolein all of which are high use pesticides. Data are needed in the area of low

level, chronic (life time) exposures. Studies should include exposure to formulated products (i.e. mixtures) as well as pure compound.

5. There should be a periodic reevaluation by newer, more sensitive and more predictive methodologies of those pesticides used in large volume.

DEFINITIONS

The Safe Drinking Water Committee adopted the following working definitions prior to its review of the scientific literature of organic contaminants:

Carcinogen. The term carcinogen is used in its broad sense, because in most of the current human epidemiologic approaches and certain animal bioassays it is not possible to differentiate clearly between initiating agents, promoting agents, and certain modifying factors. Any factor or combination of factors which increases the risk of cancer in humans is of concern regardless of its mechanism of action. The criteria listed here apply only to chemical agents.

A malignant neoplasm is composed of a population of cells displaying progressive growth and varying degrees of autonomy and cellular atypia. It displays, or it has the capacity for, invasion of normal tissues, metastasis, and causing death to the host. Benign neoplasms are a less autonomous population of cells and exhibit little or no cellular atypia or invasion of normal tissues and do not metastasize. In particular cases, however, benign neoplasms may endanger the life of the host by a variety of mechanisms, including hemorrhage, encroachment on a vital organ, or unregulated hormone production. The cytologic and histologic criteria utilized in determining whether a lesion is benign or malignant differ depending upon the tissue in which the neoplasm arises. Evaluation of whether a specific lesion is benign or malignant should therefore, follow standard criteria used by experimental oncologists and pathologists with the emphasis on correlation of the histopathologic pattern with the biologic behavior of the lesion or type of lesion. In equivocal cases, the diagnosis of a specific lesion may require a panel of experts; recognizing that they may not always agree.

Depending upon the particular case, benign neoplasms may represent a stage in the evolution of a malignant neoplasm and in other cases they may be "end points' which do not readily undergo transition to malignant neoplasms.

A. Criteria in Human Studies

An agent - which may comprise a combination of chemicals - is carcinogenic in man if it increases the incidence of malignant neoplasms (or a combinaton of benign and malignant neoplasms) in humans to levels that are significantly higher than those in a comparable group not exposed (or exposed at a lower dose) to the same agent. If all of the induced neoplasms are benign, rather than malignant, then, for the reasons given elsewhere in this document, the agent must be considered a possible carcinogen and it should, therefore, be very carefully evaluated as a health hazard.

Types of evidence suggesting that an agent is carcinogenic in humans include: neoplastic response directly related to exposure (both duration and dose); incidence and mortality differences related to occupational exposure; incidence and mortality differences between geographic regions related to different exposures rather than genetic differences and/or altered incidence in migrant populations; time trends in incidence or mortality related to either the introduction or removal of a specific agent from the environment; case control studies; and the results of retrospective-prospective and prospective studies of the consequences of human exposure. Clinical case reports may also provide early warning of a potential carcinogen. Negative epidemiologic data may not establish the safety of suspected materials. Negative data on a given agent obtained from extensive epidemiologic studies of sufficient duration are useful for indicating upper limits for the rate at which a specific type of exposure to that agent could affect the incidence and/or mortality of specific human cancers.

B. Criteria in Experimental Animal Studies

The carcinogenicity of a substance is established when the administration to groups of animals in adequately designed and conducted experiments results in increases in the incidence of one or more types of malignant neoplasms (or a combination of benign and malignant neoplasms) in the treated groups as compared to control groups maintained under identical conditions but not given the test compound. The increased incidence of neoplasms in one or more of the experimental groups should be evaluated statistically for significance, and the only major experimental variable between the control and the experimental group should be the absence or presence of the single test agent. Such increases may be regarded with greater confidence if positive results are observed in more than one group of animals or in different laboratories. The demonstration that the occurrence of neoplasms follows a dose-dependent relationship provides additional evidence of a positive result.

The occurrence of benign neoplasms raises the strong possibility that the agent in question is also carcinogenic since compounds that induce benign neoplasms frequently induce malignant neoplasms. In addition, benign neoplasms may be an early stage in a multi-step carcinogenic process and they may progress to malignant neoplasms; also, benign neoplasms may themselves jeopardize the health and life of the host. For these reasons, if a substance is found to induce benign neoplasms in experimental animals it should be considered a potential human health hazard which requires further evaluation. In experiments where the increased incidence of malignant neoplasms in the treated group is of questionable significance, a parallel increase in incidence of benign tumors in the same tissue adds weight to the evidence for carcinogenicity of the test substance (from General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances. Report of the Subcommittee on Environmental Carcinogenesis NCI, 1976).

Mutagen. A chemical which is capable of producing a heritable change in genetic material. These changes may be either point mutations or chromosomal mutations and can occur in either somatic or germ cells.

Teratogen. An agent which acts during pregnancy to produce a physical or functional defect in the developing offspring.

Organoleptic test. The use of odor and taste thresholds to establish permissible levels of exposure to chemicals.

Adverse Response. "With increasing dosage in the continuum of the dose-response relationship, the region is generally entered where the effects are clearly adverse. Thus, adverse effects may be defined as changes that:

1. Occur with intermittent or continued exposure and that result in impairment of functional capacity (as determined by anatomical, physiological, and biochemical, or behavioral parameters) or in a decrement of the ability to compensate for additional stress.

2. Are irreversible during exposure or following cessation of exposure if such changes cause detectable decrements in the ability organism to maintain homeostatis.

3. Enhance the susceptibility of the organisms to the deleterious effects of other environmental influences."

(Quoted from Principles for Evaluating Chemicals in the Environment. 1975. National Academy of Sciences, Washington, D.C.)

Toxicity. The intrinsic quality of a chemical to produce an adverse effect. The term includes capacity to induce teratogenic, mutagenic, and carcinogenic effects.

Safety. "Safety is the practical certainty that injury will not result from the substance when used in the quantity and in the manner proposed for its use."

(Quoted from Evaluating the Safety of Food Chemicals. 1970. National Academy of Sciences, Washington, D.C.).

Evaluation of Safety. "An estimation of the potential of the substance to cause injury and review and evaluation of sufficient data to warrant a conclusion that the conditions of proposed use will provide an intake so low in relation to the toxic dose that there is a practical certainty no harm can result."

(Quoted from FDA Papers, November, 1971).

For the purpose of this study the proposed use was limited only to exposure from drinking water.

Safety Factor or Uncertainty Factor. A number which reflects the degree or amount of uncertainty which must be considered when experimental data in animals are extrapolated to man. When the quality and quantity of data are high the uncertainty factor is low and when data are inadequate or equivocal, the uncertainty factor must be larger.

The follwoing general guidelines have been adopted in establishing the uncertainty factors.

1. Valid experimental results from studies on prolonged ingestion by man, with no indication of carcinogenicity.
Uncertainty Factor = 10
2. Experimental results of studies of human ingestion not available or scanty (e.g., acute exposure only). Valid results of long-term feeding studies on experimental animals or in the absence of human studies, valid animal studies on one or more species. No indication of carcinogenicity.
Uncertainty Factor = 100
3. No long-term or acute human data. Scanty results on experimental animals. No indication of carcinogenicity.
Uncertainty Factor = 1,000

These uncertainty factors are used in every case as a divisor of the highest reported long-term dose which is observed not to produce any adverse effect.

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Chapter VII

RADIOACTIVITY IN DRINKING WATER

Since it was discovered that ionizing radiation produces detrimental biological effects, many national and international groups have studied the sources and levels of radiation to which the human population is exposed, and have estimated the corresponding biological effects. Some of these groups have also been responsible for establishing permissible levels of exposure. Consequently, there is a large body of information on the biological effects of ionizing radiation. The Subcommittee on Radioactivity in Drinking Water has relied heavily on the reports of those other groups and has abstracted and summarized pertinent sections. In some cases it was possible to take new published and unpublished information into account in this assessment of the probable effects of the radioactivity in drinking water on the population of the United States.

Among the groups whose reports were used were the National Academy of Sciences Advisory Committee on the Biological Effects of Ionizing Radiation (BEIR), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the International Commission on Radiological Protection (ICRP), and the National Council on Radiation Protection and Measurements (NCRP).

BACKGROUND RADIATION

The natural ionizing radiation, to which all people are exposed, includes cosmic rays and products of the decay of radioactive elements in the earth's crust and atmosphere. Part of the terrestrial radiation dose is from sources external to the body, and part is due to the inhalation and ingestion of radioactive elements in air, food, and water. In the United States, this unavoidable background radiation gives, on the average, an annual dose of about 100 mrem to the population (Table VII-1). There is, however, great variability in the amount of background radiation, which depends on regional geological characteristics and altitude. It has been found, for example, that the annual background dose in Colorado is 100 mrem (or more) higher than that in Louisiana (BEIR Committee 1972). Mankind has always lived with such radiation, to which, however, the radionuclides in drinking water contribute but a small share.

ABUNDANCE OF RADIONUCLIDES IN WATER

Minute traces of radioactivity are normally found in all drinking water. The concentration and composition of these radioactive constituents vary from place to place, depending principally on the radiochemical composition of the soil and rock strata through which the raw water may have passed.

Many natural and artificial radionuclides have been found in water, but most of the radioactivity is due to a relatively small number of nuclides and their decay-products. Among these are the following emitters of radiation of low linear energy transfer (LET): potassium-40 (^{40}K), tritium (^{3}H), carbon-14 (^{14}C), and rubidium-87 (^{87}Rb). In addition, high LET, alpha-emitting radionuclides, such as radium-226 (^{226}Ra), the daughters of radium-228 (^{228}Ra), polonium-210 (^{210}Po), uranium (U), thorium (Th), radon-220 (^{220}Rn) and radon-222 (^{222}Rn), may also be present in varying amounts.

Natural Radionuclides

Sources of Low-LET Radiation. Some of the radionuclides that are responsible for the natural radioactivity in drinking water come from radioactive elements, and their decay-products, that were incorporated in the earth at its formation, and others are produced continuously by cosmic ray bombardment. Tritium is produced by cosmic ray interactions with atmospheric oxygen and nitrogen. It is then oxidized to tritiated water, which mixes into the hydrosphere. Tritium concentrations in water supplies vary from about 10 to 25 pCi/liter (Jacobs, 1968).

In similar fashion, carbon-14, produced by cosmic ray ($^{14}N(n,p)^{14}C$) interactions with atmospheric nitrogen (UNSCEAR, 1972, p. 29), is oxidized to $^{14}CO_2$, which is generally found at a concentration corresponding to about 6 pCi ^{14}C per gram of carbon. In water containing about 1 mg of carbon per liter, a concentration of 0.006 pCi/liter might be expected. In ocean water, the concentration might be about 0.1 pCi/liter (NCRP 1975, p. 15).

Of all the natural radionuclides that occur in water and emit low-LET radiation, potassium-40 is likely to be the most significant. This primordial radionuclide occurs as a constant percentage (0.0118%) of total potassium. Adults in the United States ingest about 2,300 pCi of potassium-40 per day, but almost all of it is derived from foodstuffs. Since potassium concentrations in man seem to be under homeostatic control, wide fluctuations in drinking-water potassium would have negligible effects on internal concentrations. Assuming that there is 0.2%

potassium in soft tissue, a dose rate of 19 mrad per year has been estimated; of this, 17 mrad are due to beta radiation (UNSCEAR, 1972, p. 30). In 1970, California drinking water, for example, contained up to 4 pCi/liter of potassium-40. Consumption of two liters per day of such water might contribute as much as 8 pCi per day, but this is a negligible fraction of the total daily intake of 2,300 pCi of a nuclide that is the largest natural contributor to total body somatic and genetic dose.

Sources of High-LET Radiation. Radionuclides that are produced by the decay of uranium-238 and thorium-232 are widely distributed throughout the earth's crust. The majority of them are alpha-emitters and include isotopes of polonium, radon and radium (UNSCEAR, 1972, p. 31). Concentrations of uranium in drinking water are extremely variable, apparently ranging from 0.02 to 200μg/liter in fresh waters. The thorium content of drinking water has not been extensively measured, but its concentration in the human skeleton is about 1 fCi/g of ash; the corresponding abundance of uranium in the skeleton is about ten times greater.

The natural alpha-emitters that occur in drinking water appear to be bone seekers. Of these, radium-226 and its daughters, and the daughters of radium-228 probably have the greatest potential for producing radiation doses of some consequence to man. The radium-226 content of fresh surface water is variable, ranging from 0.01 to about 0.1 pCi/liter. Some ground water may contain up to 100 pCi/liter. Drinking water obtained from surface supplies generally does not contain significant amounts of radium, and treatment processes such as flocculation and water-softening, can remove the bulk of radium from water.

In the Midwest of the United States there is an area where ground waters contain significant levels of radium-226 and radium-228. This area--primarily in Iowa, Illinois, Wisconsin, and Missouri--includes an estimated population (1960 census) of approximately 1 million persons. The weighted mean concentration of radium-226 has been estimated to be approximately 5 pCi/liter (Peterson et al. 1966). Rowland, Lucas, and Stehney (1975) have reported that approximately 500,000 people in Illinois and Iowa have drinking water supplies whose radium-226 content is 3-6 pCi/liter; about 300,000 people, 6-9 pCi/liter; and about 120,000 people live in areas where well water contains 9-80 pCi/liter of radium-226. A personal communication (Rowland, Lucas, and Stehney, 1976) from the same investigators stated that, of the last group, 113,000 people drink water that contains less than 20 pCi/liter, and 5,200, 20-25 pCi/liter. The one community (1,200 persons) that had a well in which 80 pCi/liter of radium-226 were found now uses water from a well containing only 3 pCi/liter.

In addition, a survey in 1966 that was designed to locate water supplies with high concentrations of radium, found water supplies with more than 3 pCi of radium-226 per liter in areas other than those of the northern Midwest described above (Hickey and Campbell, 1968). These supplies served approximately 145,000 people. Thus, it appears that in the entire United States approximately 1.1 million people consume water that contains more than 3 pCi/liter of radium-226.

The major additional contribution to the alpha-emissions in drinking water is due to the decay of radium-228; although other alpha-emitting natural radionuclides have been found in drinking water, they occur in exceedingly small concentrations. For example, one analysis of water containing 5 pCi of radium-228 per liter was found to contain less than 0.02 pCi/liter of thorium isotopes and only 0.03 pCi/liter of uranium (Stehney, 1960).

Two other radium isotopes may be present in drinking water, but although both radium-223 and radium-224 may contribute to the gross alpha activity of water measured very soon after drawing from the tap, their contributions to the long term dose deposited in the skeleton are negligible because they have short half-lives. However, radium-228, which decays by beta emission, and therefore does not contribute to gross alpha activity in drinking water, will, as a result of its subsequent decay scheme, give rise to a series of alpha-emitting daughter products. It is these radium-228 daughter products, and radium-226 and its daughters, that produce, in our opinion, the major alpha-particle dose to the tissues of the body, particularly to the skeleton. Thus, when discussing radium in drinking water, it is essential to distinguish between the isotopic mixture measured in freshly drawn drinking water and the long-term alpha dose that might be accumulated in tissue.

Because of the different decay schemes for radium-226 and radium-228, different alpha doses are received under equilibrium conditions from each of these two radium isotopes. In waters of low alpha-particle radioactivity, the activity concentration of radium-228 is generally equal to that of radium-226, whereas at high radioactivity concentrations it is only half that of radium-226 (Lucas and Krause, 1960).

The abundance of the radioactive gas radon-222, that is formed by the decay of radium-226, is not highly correlated with the radium concentration in fresh water. Radon concentration is generally 1 pCi/liter in surface water, but activity concentrations in ground water are typically a few thousand times greater. Some mineral or spa waters, however, may contain 500,000 pCi/liter.

Consumption of water containing 1 µCi of radon-222 will result in a stomach dose of about 20 mrads, but the doses to other organs will be lower by at least a factor of ten (UNSCEAR 1975, p. 35). Furthermore, consumption of 2 liters per day of water containing 1 nCi/liter of radon-222 would deliver an annual stomach dose of about 12 mrad.

In three large American cities, the total daily intake of uranium, radium-226, radium-228, and lead-210 in water have all been quoted to range approximately between 0.01 and 0.05 pCi/day (NCRP 1975, p. 92). When compared with other components of the diet, drinking water usually contributes less than about 2% of these alpha-emitting radionuclides to the daily dietary intake (NAS-NRC, 1973). The greatest dose potential from alpha-radiation from naturally occurring radionuclides in drinking water will be related to the ingestion of radium-226 in areas where its concentration is high.

Artificial Radionuclides

To some extent, all drinking water obtained from surface sources will reflect contamination from atmospheric testing of nuclear weapons. Extensive measurements have been made of the contribution of airborne fission products to drinking water contamination and in particular to the levels that were produced by testing weapons before the Nuclear Test Ban Treaty of 1963. The sharp decrease in radioactive fallout since that date has been followed by a corresponding decrease in the radioactivity of surface water. Although the analyses are not very extensive, the temporal characteristics provide some information that is useful in predicting the transport and fate of radionuclides in water. Some of the longer-lived radionuclides still persist from early tests, together with smaller quantities of fission products injected irregularly into the atmosphere from the testing of weapons by non-treaty nations.

Many of the states conduct periodic surveys of the radioactivity of drinking water. Unfortunately, these consist, for the most part, in counting only the gross beta and gross alpha activity in the water. In addition, there is a considerable body of data on the temporal patterns and regional concentrations of the fission products strontium-90 and cesium-137, the physical half-lives of which are about thirty years.

There appears to be a fairly good correlation between the measurement of solids in finished water and radioactivity content measured as beta activity (Fig. VII-1). It is likely that potassium-40 in soil suspensions might account for such an observation. Because they account for a major part of the potential dose from nuclear fission and activation products, and because of their biological significance, considerable attention has been devoted to strontium-90, cesium-137, iodine-131, tritium and carbon-14, as potential water contaminants. These, however, are not necessarily correlated with the solids content of drinking water.

Sources of man-made radionuclides, in addition to atmospheric weapons tests, include local discharge of radiopharmaceuticals and the possible entry of radioactivity into watersheds from the use and processing of nuclear fuel to produce electric power.

Radiopharmaceuticals. The release of radioactive materials in the exhaust air and liquid wastes from medical institutions has been studied many times in different locales. No evidence yet suggests a drinking-water hazard from medical effluents. This conclusion is based on data collected in many surveys (Sodd *et al.*, 1975, Gesell *et al.*, 1975; Klement *et al.*, 1972; Kaul and Loose, 1975). The agents to which particular attention was given in these surveys were radioactive iodine and technetium-99m. Both are widely used in medical practice, and there is special concern over the iodine isotopes, because of their potential effects on the thyroid gland.

Since 1950, eight groups have reported on the extent of release of radioisotopes in areas of the United States where there were active clinical nuclear medicine programs. Because of recent rapid increases in the numbers and kinds of procedures being conducted, Sodd *et al.* (1975) studied the use and discharge of iodine-125, iodine-131, and technetium-99m in the Cincinnati area. They measured the radioactivity from these nuclides in the influent, effluent, and sludge at the sewage treatment plant, as well as the activity in the Ohio River ten miles above and five miles below the plant. Gesell *et al.* (1975) conducted a similar survey of medical usage and concentrations in sewage of iodine-131 and technetium-99m in the Houston area. The general conclusions reached by both groups indicated that the effect on levels of radioactivity in drinking water of the medical usage of radioisotopes that they studied appears to be of negligible importance.

The Cincinnati study was centered about the largest sewage treatment plant serving that city. This plant receives the effluent from 10 hospitals that use radionuclides in clinical nuclear medicine. Approximately 60% of the patients were outpatients, so control of biological wastes was not attempted. Radioactivity in the sludge accumulated at the plant exceeded that in the water. Sludge concentrations of iodine-131 and technetium-99m were measurable, but that of iodine-125 was below the limit of detectability (10 pCi/liter).

It was estimated that between 10% and 30% of the total amount of technetium-99m given to patients in Cincinnati hospitals was discharged in sewage effluent into the Ohio River. Typically, about 300 mCi/week of this nuclide were estimated to reach the river, where dilution with river water was calculated to give concentrations downstream of about 1 pCi/liter. In fact, analysis of river water showed identical values upstream and downstream of 3-4 ± 3 pCi/liter. These are lower, by a factor of about a million, than the current maximum permissible concentration (6 μCi/liter, NRC 1976) of technetium-99m in water for the general population. Comparable results were obtained for iodine-131. Smaller amounts were used, and the concentrations in sludge and water were lower than those of technetium. No differences between upstream and downstream levels were detected. Under the assumption that the same dilution had occurred, the medical uses of iodine-131 in the area were calculated to produce a maximal increase in concentration in the river of about 0.1 pCi/liter. This value is about one thousandth of the current maximum permissible concentration of iodine-131 in water (300 pCi/liter, NRC 1976) for the general population.

Thus, at present, given current rates of use, patterns of disposal, and radiation protection guidelines, many orders of magnitude separate the concentrations of radioactivity in drinking water due to medical uses of radioisotopes from conceivably hazardous levels. Projections of the rate of increase in use of radiopharmaceuticals have been made by the Environmental Protection Agency (Klement et al., 1972). They estimate that there may be a twelve-fold increase in the medical use of these agents by the year 2000, on the basis of the annual increments in whole-body radiation dose from the use of these agents in medicine. This represents a very small incursion, and probably will not be measurable.

Nuclear Fuel Cycle Activities. Among the major effluents from the use and processing of nuclear fuel are tritium, plutonium, and krypton. Of these, only tritium, which is released as a gas, and plutonium can possibly enter water supplies. The predominant form of plutonium release from nuclear power and processing plants is as an aerosol that will have little or no impact on drinking water. Although a single incident has occurred in which as much as 18,750 Ci of plutonium were released from liquid storage on a local basis, none apparently reached off-site water supplies (AEC 1974, pp. 49-50). The usual rate of release from liquid storage at controlled sites is about 1 mCi/year. Continuing improvement in methods of storage should further reduce this rate. Nevertheless, the adequacy of monitoring water supplies in the vicinity of nuclear facilities should be reviewed periodically.

Because of its exceedingly long half-life (1.7 × 10^7 years), the possible consequences of the release of iodine-129 during nuclear fuel reprocessing were considered. This radionuclide has a specific activity of about 173 µCi/g of ^{129}I. In a recent review, Soldat (1976) calculated that the maximal isotope ratios of ^{129}I: ^{127}I would be about 10^{-4} in water near nuclear facilities. His calculations indicate that consumption of 2 liters/day of water containing iodine-129 at 1 pCi/liter deliver an annual thyroid dose of about 5 mrem to an adult and about 10 mrem to an infant. Peak activities in water have been reported at about 0.01 pCi/liter, which would correspond to an annual thyroid dose of about 0.05 mrem to an adult.

RADIATION DOSE CALCULATIONS

Estimates of the radiation doses expected to be produced by radionuclides ingested in water were calculated by means of the methods and parameters given in NCRP Report 22 (NBS Handbook 69, 1963 revision) and ICRP Publication 2 (ICRP, 1960). To approximate the equilibrium levels that take into account buildup, retention, decay and elimination of various radionuclides, annual doses were computed for the 50th year of constant intake of 1 pCi/year, and 2 liters per day of water containing 1 pCi/liter. These doses are presented in Table VII-2. At earlier times, the annual doses may be lower than those shown, and for a few long-lived radionuclides (e.g. ^{90}Sr, ^{226}Ra), they may never reach equilibrium, but the values in Table VII-2 are within 20% of the theoretical equilibrium levels. These values were obtained by using the NCRP and ICRP metabolic and dosimetric models for all radionuclides, except for the isotopes of the alkaline earth elements radium and strontium, which are discussed below.

Isotopes Of Alkaline Earth Elements

For the alkaline earth elements, the recent metabolic model of ICRP Publication 20 (1973) was used.

In its 1959 report on permissible doses (ICRP, 1960), * Committee II of the ICRP used an exponential model of retention for all radionuclides to calculate maximum permissible concentrations in water. The committee pointed out, however, that there was good evidence that retention of radium-226 and other bone-seeking radionuclides is best represented by a power function model (Norris et al., 1958). In the case of radium-226, the calculated body burden from intake at constant daily rate for 50 years is about a factor of 10 smaller by the power function model than by the ICRP exponential model. This may be shown by use of the equations and the values for metabolic parameters that are given in the ICRP report. Ingestion of 1 pCi of radium-226 per day in water is assumed in the sample calculations given below.

According to the ICRP exponential model, the amount of a radionuclide, qf_2, that accumulates in an organ from constant ingestion rate, a, is given by:

$$qf_2 = af_w \frac{T}{0.693}(1 - e^{-0.693\,t/T})$$

Where q = total amount in the body,
f_2 = fraction of q in the organ of reference (0.99 for bone),
f_w = fraction of radionuclide ingested in water that reaches the organ (0.04 for bone),
T = effective half-life (1.6×10^4 days)
and t = duration of ingestion, days.

For uptake of ^{226}Ra by the skeleton in 50 years,
$q\ (0.99) = (1)\ (0.04)\ (1.6 \times 10^4)(1 - 0.459)/0.693$ and the body burden q = 510 pCi for t = 18,250 days. It has been suggested that the effective half-life of ^{226}Ra is 17.1 years (Miller and Finkel 1968); the calculated body burden in the above example would then be somewhat smaller, 315 pCi.

In the case of the power function, the body burden, q, after an amount, a, of a long-lived radionuclide has been ingested per day for t days is given by:

$$q = \frac{Aaf_1}{1-n}\,t^{1-n}$$

where f_1 = fraction of ingested radioactivity that transfers from the gut to the blood (0.3), and A and n are the power-function constants for the fraction (R) retained at t days after a single

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*The maximum permissible concentrations of radionuclides in ICRP 1960 and NCRP 1963 are identical.

injection ($R = At^{-n}$). Norris et al. (1952) give the values A = 0.54 and n = 0.52.

Hence, for uptake of ^{226}Ra in 50 years,

$$q = \frac{(0.54)(1)(0.3)(18,250)^{0.48}}{0.48}$$

and the body burden q = 37 pCi. It should be noted that the power function, in the form given here, deals only with the total body burden; it is silent on the question of organ distribution.

Since 1959, additional data have tended to support a power-function model for bone-seekers. In 1972, a task group of Committee II of the ICRP presented a detailed model of alkaline earth metabolism that evolved from the power function (ICRP 1973). For a constant rate of intake into the blood for 50 years, the newer model predicts a whole-body content that is only 5% less than the simple power function given above.

Measurements of radium-226 body burdens and dietary intake at environmental levels also indicate that the ICRP exponential model predicts long term retentions that are too high. The average body burden of radium-226 in areas of normal radioactivity is about 50 pCi (40 pCi in the skeleton and 10 pCi in soft tissue; UNSCEAR 1972, p. 32). Intake of radium in food appears to be the main source at normal levels, because the average daily intake in the United States is about 1 to 2 pCi in food and less than 0.1 pCi in water (NCRP 1975, p. 92).

A quantitative relationship between the body burden of radium-226 and the concentration of radium in drinking water was found by Lucas (1961). He measured the radium content of samples of bone and soft tissue from individuals with lifetime (or at least 30 years) residence in their communities. He also measured the radium content of the water supply of each community. The average body burden of radium-226 was 36 pCi (42 persons) in cities with less than 0.1 pCi/liter, and higher body burdens (33 persons) were found in cities with 0.13–10.5 pCi/liter. With the assumption that intake of radium in food contributed 36 pCi to the total body burden of each person measured, the following relationship was found: $B = 36 + 50C_w$, where B is the total body burden (pCi) and C_w is the concentration of radium-226 in drinking water (pCi/liter). This relationship was confirmed in later work on 19 other persons of known and stable residence (Lucas et al., 1964).

It should be emphasized that the Lucas equation is an empirical relationship between body burden and the concentration of radium-226 in the local water supply. Daily rates of intake, transfer from gut to blood, etc., were not known nor taken into account. If one assumes daily ingestion of 1-2 liters of local water for the persons analysed, then the long-term accumulation of body radium from radium in water was 25 to 50 times the daily intake of radium in water. These values are compatible with ratios of body burden to daily intake that were estimated in other work (Stehney and Lucas, 1956; ICRP, 1973).

Combining the Lucas equation with the standard rate of water consumption, 2 liters/day (NCRP, 1963; ICRP, 1974), gives good agreement with the new model of alkaline earth metabolism (ICRP, 1973). According to the model, f_1 has a value of 0.21 and the body burden accumulated from daily ingestion of 2 pCi of ^{226}Ra for 50 years is 50 pCi, of which 41.5 pCi is in bone.

Since the relevant metabolic parameters for radium-228 are the same as for radium-226, the ICRP power function model may also be used to calculate long-term retention of radium-228. For ingestion of 2 pCi/day for 50 years, the calculated body burden of radium-228 is 21 pCi (14.2 pCi in bone). The dose factors given in Table VII-2 are based on effective absorbed energies per disintegration of 106 MeV for radium-226 and 301 MeV for radium-228 (NCRP, 1975)

The metabolic model of ICRP Publication 20 (1973) was also used to calculate the retention of radiostrontium from continuous ingestion in water. For strontium-90, the calculated body burden from ingestion of 2 pCi/day for 50 years is 229 pCi, of which 222 pCi are in bone; for strontium-89, the corresponding values are 7.6 pCi and 5.0 pCi. The effective absorbed energies of the strontium isotopes in bone and total body given in ICRP 1960 were used to calculate the dose factors shown in Table VII-2.

Doses From Water of Specified Composition

To illustrate the doses to be expected from drinking water that may be typical of the United States generally, a hypothetical water supply was postulated to have the amounts of radioactivity shown in Table VII-3. Also tabulated are the corresponding annual doses to be expected in the 50th year of constant consumption of 2 liters/day of this water, as calculated with the dose factors of Table VII-2.

The concentrations in Table VII-3 were chosen to represent the average tritium concentration, beta activity, and alpha activity of the water analyses reported in the Environmental Protection Agency's 1975 Report to Congress (EPA, 1975). The average tritium concentration was found to be 250 pCi/liter (p.

IV-4). The average beta activity (excluding tritium) from all interstate carrier water supplies--for which figures were reported for gross beta, gross alpha, strontium-90, and radium-226 activity--was 3.1 pCi/liter. The gross alpha activities for the same samples were less than 2 pCi/liter in all but one case. The reported detection limit for gross alpha was 2 pCi/liter, and for strontium-90 beta activity, 0.5 pCi/liter. In these samples, many of the entries were below this detection limit. Almost all samples were below 1 pCi/liter. A reasonable concentration of strontium was therefore taken to be 0.5 pCi/liter. Radium-226 concentration in these samples averaged about 0.2 pCi/liter (two of the entries in the EPA report were incorrectly given as 9.12 and 9.10, instead of 0.12 and 0.10).

In addition to the tritium and strontium-90 concentrations noted above, it was assumed that the other major beta-contributors would be potassium-40, cesium-137, and radium-228. Cesium-137 in drinking water in the United States is currently derived primarily from fall-out from atmospheric weapons testing. As "surface" depositions, the concentrations vary. They are likely to be higher in surface water than in ground water. Values for this nuclide are not available for all the states; and even within a single state (e.g., California), concentrations are variable. A plausible concentration of this nuclide was estimated to be 0.1 pCi/liter. Equally variable, but for reasons related more to geology than to anything else, is the concentration of radium-228. It was assumed that the radium-228 concentration is approximately equal to that of radium-226, and for this hypothetical example a value of 0.2 pCi/liter was adopted (Stehney and Krause, 1960). Finally, potassium-40, which is ubiquitous in water supplies, is also variable; in the absence of any nationwide surveys of its concentration, it was concluded, from the range of concentrations in California (Goldberg, 1976), that 2.1 pCi/liter would be a reasonable estimate for the hypothetical water composition.

Calculating a gonadal dose for bone-seeking radionuclides is difficult. Strontium-90, for example, when fed continuously to dogs, was found to be one thousand times less concentrated in gonadal tissue than in bone. It could then be estimated that a bone dose of 0.1 mrem/yr might be accompanied by a gonadal dose of about 0.1 µrem/yr (Della Rosa _et al._, 1972).

Unfortunately, extensive analyses of specific radionuclides other than radium-226, strontium-90, and tritium in water are not available. Dose factors for the majority of known radionuclides derived from NCRP Report 22 (1963), are given in Soldat _et al._ (1975), and may readily be used to calculate annual doses when new analytical results are obtained.

A spectrometric analysis of a 1974 drinking water composite from Los Angeles became available (Goldberg, 1976), and was used to construct another illustrative example as shown below. The potential doses, assuming 50-year constant intake at 2 liters/day, were calculated as in the previous example.

Nuclide	Concentration pCi/liter	Potential Doses (mrem/yr) Total Body	Organ
^{40}K	5.20	0.09	
^{54}Mn	0.48	0.006	0.005 (GILLI)
^{90}Sr	0.09	0.0002	0.6 (Bone)
$^{95}Zr-^{95}Nb$	0.61	0.000003	0.1 (GILLI)
^{137}Cs	0.05	0.003	
^{144}Ce	0.21	0.000004	0.03 (GILLI)
^{226}Ra	0.05	0.014	0.8 (Bone)

In this case, a total bone dose of 2 mrem/year would be calculated (although not separately determined in this analysis, an amount of α-activity from radium-226 daughters nearly equal to that of the radium-226 would also be expected). For all other tissues, including the gonads, the annual dose would be about 0.12 mrem.

ESTIMATION OF RISK

Developmental and Teratogenic Effects

On the basis of numerous studies on the effects of external radiation, it has become generally accepted that developing mammals (intrauturine and juvenile) are more radiosensitive than adults (BEIR Committee, 1972; Sikov and Mahlum, 1969). Since the basic interactions of radiation do not differ with age, it appears that the increased sensitivity follows from the high rates of cell proliferation and the complex interactions associated with development. Also, the variety of integrated developmental stages, through which the immature organism must progress to attain maturity, increases the chance that derangements will occur.

In general, these deleterious effects may be divided into three categories: increased tumor incidence, death, and developmental abnormalities. The first category is discussed later and will not be considered here. In the broad sense, the last category includes physiological and biochemical deficits and deviations, as well as malformations. Most of the quantitative dose-effect relationships have been derived from studies using relatively high radiation doses from external photon beams.

The doses required for embryolethality change during development, and vary by more than a factor of ten. There are also short "critical periods" for most, if not all, malformative events. Most of the available data suggest an apparent threshold at about 10 rads of acute exposure and a sigmoid dose-response relation for production of lethality and developmental abnormalities (BEIR Committee, 1972; Brent and Gorson, 1972). It is possible, however, that this value may be overestimated since there are relatively few observations at low doses and there is a lack of satisfactory methods for detecting minimal defects. Many of the observed morphological malformations have been hypothesized to involve a reduction in cell number to a value below some critical level as an early step in the pathogenic process. These considerations would offer a theoretical explanation of the apparent threshold for radiation teratogenesis.

The difficulties inherent in extrapolating the results of experiments at high doses and high dose rates, to low doses and low dose rates include those applicable to the adult as well as some that are specific to the immature organism. In general, protracting the dose from low-LET radiation results in a decreased biological effect. For developmental effects, the influence of protraction of exposure is even greater because only a small fraction of the life span is spent in the susceptible prenatal and neonatal stages. Only radiation that is absorbed during the critical period of hours or days would be effective in altering the particular processes occurring at that time.

Because of the apparent existence of thresholds, nonlinearity, and critical periods, risk estimates calculated in terms of events per rem are not meaningful at low doses and dose rates. Because of this and because of the available data, it may be expected that low doses of radiation delivered at low dose rates would have a small likelihood of being embryotoxic (embryocidal or teratogenic). Despite these limitations, the most pessimistic case for embryotoxicity can be calculated from the estimated threshold dose of 10 rads of acute radiation. If the 10 rads were protracted over the 9 months of gestation and the first year of life a daily dose of about 15 mrads would result. The conservatism of this estimate is suggested by the fact that the lowest dose of protracted external radiation for which confirmed deleterious effects have been reported (defective development of some organs and decreased life span, but no acute mortality) is slightly over 1 rad per day throughout late gestation and early postnatal life (BEIR Committee, 1972). It has been recently reported (Cahill et al., 1976), however, that a radiation dose of 1 mrad per day to the conceptus from continuous ingestion of tritium by pregnant rats produced a slight, but statistically significant, delay in eye-opening and development of the righting reflex.

It should be noted that the water intake of the neonate is initially minimal, increasing with time. Even in the juvenile period, milk (from commercial or maternal sources) is often the major source of fluid, and it reflects, to some extent, the radionuclide content of the water supplies and food.

The exposure of the fetus to radionuclides depends on the maternal body burden, and particularly on the concentrations of radionuclides in the maternal circulation; the fraction available to cross the placenta depends on the rate of removal from the circulation. The amount of activity to which the conceptus may be exposed is also a function of the facility with which the nuclide crosses the placenta. Radioisotopes of normal dietary constituents generally behave as do the stable isotopic species and there are extensive data on many contaminant radionuclides (Sikov and Mahlum, 1969; Brent and Gorson, 1972). Availability is influenced also by the chemical and physico-chemical form of the nuclide and changes with the stage of gestation. Most elements, in their usual forms, fall into three broad categories relative to cross-placental transfer. The first category includes materials--such as phosphorus and iodine--that freely cross the placenta, either by rapid diffusion or by active transport, and reach fetal blood concentrations approximating those of the mother. Tissue concentrations depend on metabolic considerations and may influence the rate of removal from the blood. These processes are age-dependent, in that it is not until thyroid function or skeletal calcification begins that significant quantities of iodine or strontium are removed from the circulation. At these times, the fetal concentrations in the target organs may slightly exceed those in the mother, although they are often smaller. The second category encompasses the many elements that diffuse relatively slowly and may include those for which there appear to be placental barriers to their transfer. The third category consists of the elements that themselves or in their usual chemical form are poorly transferred to the conceptus. The average concentration of such a material in the fetus is only a small fraction of that in the mother, although specific tissue concentrations occasionally approach maternal values (Wrenn, 1975). For some of these elements (e.g., ^{239}Pu) it appears from rodent studies that most of the embryotoxicity early in gestation is attributable to material localized in the villus yolk sac (Sikov and Mahlum, 1972). Because this structure is vestigial in man, it is uncertain whether this finding has significance for exposure of humans.

On the basis of the foregoing, and the calculations of potential radiation doses, we anticipate that no measurable developmental and teratogenic effects of radionuclides in drinking water will be found at the levels studied.

Genetic Effects

Many national and international groups (BEIR, NCRP, ICRP) revise from time to time our understanding of the genetic risks to human populations from ionizing radiation. The estimates of genetic effects of low levels of radiation due to ingestion of radioactive isotopes in drinking water that follow this section are based on their work.

Mutations--changes in the genetic information--can occur at any time in any cell of the body. Geneticists, however, are concerned primarily with mutations that occur in the genes and chromosomes of germ cells, sperm and eggs, or the cells from which they are derived. Sperm and egg cells, after fertilization, give rise to the individuals of the next and later generations. Thus, a mutation originating in germ cells could, in time, spread through the population.

From the earliest studies on mutation it was recognized that the vast majority of newly arising mutations were, in varying degrees, detrimental. If this seems paradoxical in an evolutionary sense, it should be noted that evolution proceeds by selection of individuals with the highest reproductive fitness, fixing beneficial mutations and generally eliminating less favorable ones. This selection process is not perfect, and harmful mutants do spread into the population until they are eventually eliminated through death, sterility, or reduced fertility. In some cases, on the other hand, unusual selective phenomena have led to the maintenance of genetically determined diseases, such as sickle cell anemia, in which the genetic carriers are resistant to malaria. In general, however, the more severe the mutation, the more rapid is its elimination; indeed, a substantial proportion is most likely eliminated without notice in early pregnancy. Conversely, mutations that impair the vigor of individuals only slightly might penetrate a population over a long period of time before selection occurs.

Mutations arising in non-germinal or somatic cells are limited to expression in the individual and cannot be transmitted to future generations. They are nevertheless of considerable importance, in that the induction of many cancers may be related to mutation induction. For instance, studies indicate that approximately 90% of organic compounds that are carcinogens are also mutagens (McCann et al., 1975; McCann and Ames, 1976).

Mutations fall into three major categories of genetic alteration: gene mutations, chromosome aberrations, and changes in chromosome number. Gene mutations, in which the genetic change is restricted to a submicroscopic region of a chromosome, affect only a rather restricted amount of the cell's information content. For example, mutations in the gene controlling the production of hemoglobin in red blood cells might be manifested as an altered or missing hemoglobin. Such a mutation might have no bearing on the manner in which the hemoglobin functions or it might be the cause of severe anemia as in sickle cell anemia.

In the fertilized egg, chromosomes and genes (with the exception of sex chromosomes and their genes) are inherited in pairs, one member of the pair coming from each parent. Mutant genes are usually described by the manner in which their activity is manifested. A dominant mutation or gene is one that gives an altered effect (or phenotype) in the presence of a normal partner gene. A recessive mutant gene is one whose effect is apparent in the individual only if both members of the pair of genes are mutant; when the recessive and normal are both present, the mutant trait does not appear. Sex-linked recessive genes--those on the X-chromosome--govern traits more commonly observed in males than in females. Males have only one X-chromosome, whereas females have two; thus, the phenotype resulting from a recessive gene on the male's X can be expressed, whereas, in females, unless both X-chromosomes contain the recessive, it cannot. Some gene mutations are caused by the deletion of a single base pair within the gene. In practice, it is usually difficult or impossible to discriminate between gene mutations and deletions that extend beyond the borders of a single gene to neighboring genes. If the deletions are microscopically invisible they will usually be classified as simple gene mutations.

Deletions may vary in scale from the loss of a single base pair to larger losses that extend into the second major category of genetic change: Chromosome aberrations. This category encompasses alterations in chromosomal structure that are visible under the microscope. Recognizable aberrations include deletions of chromosomal segments, additions of segments, and changes in the position of segments, either within a single chromosome or between two or more chromosomes. These changes can have considerable biological consequences in that the health, survival, and reproduction of individuals with such altered chromosomes might be impaired. Although these individuals might appear normal, their offspring could be severely afflicted as a result of the reshuffling of the genetic information that routinely occurs in the formation of new germ cells.

The third category of mutation consists of changes in the number of whole chromosomes in the genetic set carried in the germinal cells. In man, each germ cell contains 23 chromosomes, the fertilized egg and the individual produced therefrom has 23 distinctly recognizable pairs of chromosomes in each somatic cell. With the exception of the X-and Y-chromosomes of the male, the members of each pair are morphologically alike.

During meiosis, the process of germ cell formation, the chromosomes are redistributed, so that each germ cell will contain only one member of each pair. During this redistribution, mistakes sometimes occur, and some cells receive two members of a pair. Correspondingly other cells receive neither member. When these aneuploid cells (cells with abnormal numbers of chromosomes) are involved in fertilization, the most commonly observed consequence is prenatal death. In a small number of cases, survival associated with severe congenital abnormality occurs. Examples of this are Down's syndrome, Edwards' and Patau's syndromes, and various sex-chromosome anomalies. About 0.5% of all live born children contain an improper chromosome number and since more than 1 million babies are born in the United States each year, this is a substantial number of severely handicapped children.

It should be mentioned that many cases of genetic disease in man result, not from single genes, but from the concerted actions of many genes (multifactorial traits). Strictly speaking, a mutation in one of the many genes does not necessarily influence the manifestation of disease. Because of the complexity of the genetics associated with these diseases, our understanding both of their nature and of their response to mutation is very limited.

All the forms of genetic change described above (see Table VII-3 for examples) are known to occur spontaneously, i.e., in the absence of known causative agents. They also can be produced by various physical agents, such as ultraviolet light and ionizing radiation, and by chemical agents. Whether or not naturally occurring mutagens in our environment are responsible for the "spontaneous" mutation rate is moot. Certainly no single agent can readily be implicated as the sole cause. Present evidence indicates that natural background radiation levels (from cosmic rays and natural terrestrial radioactivity) are able to account for only part of the spontaneous incidence.

Although there is no definitive proof that any single mutant human individual resulted from exposure of the parents to a known mutagen (radiation or chemical), and thus no direct proof that these agents are indeed mutagenic in man, radiation has been demonstrated to be mutagenic in so many organisms that it seems very unlikely that it is not mutagenic in man. In fact, all the various types of mutations described above have been induced in cultured human somatic cells. The question, therefore, is not whether mutations will be induced, but rather how many will be introduced into the population.

Basis for Estimating Genetic Risk in Man. Three major principles of particular relevance to human risk estimates have emerged from studies of induced mutation.

1. Radiation or other mutagens appear to produce genetic changes that are qualitatively the same as those that occur naturally. Different mutagens, however, may not increase all types of mutations in quantitatively the same manner.
2. At low doses and low dose rates of low-LET radiation, mutations are induced in direct proportion to the dose. No threshold dose is evident in the experiments testing this (with a few exceptions that are presently the subject of reevaluation).
3. In the low dose range of irradiation to which human populations are normally exposed from natural background or man-made sources, the manner in which the dose is received will not affect the yield of induced mutations. The same number of

mutations will result if one hundred millirem are received all at once or spread out over weeks, months, or even years.

As mentioned earlier, national and international groups (ICRP, NCRP, UNSCEAR) have periodically evaluated the data and provided recommendations based on their assessments of radiation hazards. In the United States the National Academy of Sciences in 1972 published a major document, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. This report (BEIR Committee, 1972) serves as a principal source of guidance for such governmental agencies as the Environmental Protection Agency, the Nuclear Regulatory Commission, etc., that are charged with protecting the public from unnecessary exposure.

The BEIR Committee report is the major basis for the risk estimates reached here. In addition, because of evidence that has become available since the publication of that report, some modifications will be considered.

The Subcommittee on Genetics of the BEIR Committee used four ways to estimate the risk:

1. Risk Relative to That from Natural Background Radiation.

The average natural background radiation level in the U.S.A. is about 100 milliroentgens/year. The Committee noted that by keeping the additional radiation dose to the population from man-made sources below this level "we are assured that the additional consequences will neither differ in kind from those which we have experienced throughout human history nor exceed them in quantity". Thus, the BEIR Committee recommended that the natural background radiation be used as a standard of comparison.

2. Risk Estimates for Specific Genetic Conditions.

To determine the risk, The BEIR Committee made estimates of the doubling dose for human mutation rates, i.e., the dose required to double the spontaneous mutation rate. These values were obtained by dividing the best estimates of human spontaneous gene mutation rates by the average induced mutation rate per gene (or locus) per roentgen, which was obtained from mouse germ cell studies. The average human rate was taken to be between 0.5×10^{-6} and 0.5×10^{-5} per gene per generation. The induced average gene mutation rate for spermatogonia was taken as 0.5×10^{-7} per rem, while that for oocytes was taken as zero and the two were averaged as 0.25×10^{-7}. The doubling dose for gene mutation was therefore taken to be between 20 and 200 rem ($0.5 \times 10^{-6}/0.25 \times 10^{-7}$ and $0.5 \times 10^{-5}/0.25 \times 10^{-7}$). The genetic conditions and their spontaneous incidences were taken from studies carried out in Northern Ireland up to 1958. Thus, the estimates of risk are themselves based on three separate estimates, each of which has some degree of uncertainty. The results of the BEIR analysis are presented in Table VII-5. The estimates are presented in terms of effects in the first generation and effects at equilibrium when the maximum permissible dose (5 rem over a 30 year generation time) is given for many generations.

The BEIR Committee based its estimates of the number of radiation-induced chromosome anomalies resulting from unbalanced chromosome rearrangements on the frequency of balanced translocations recorded as semisterility in the offspring of male mice whose spermatogonia had been irradiated. For chronic irradiation at low LET and low dose rates, this frequency was taken to be 1.5×10^{-5} per rem. To convert to human terms, this value was multiplied by 2 to correct for the greater sensitivity of human chromosomes, multiplied by 4 to estimate the number of unbalanced translocations, and multiplied again by 2 to include an equivalent rate induced in females (since that value was unknown). This product, multiplied by 5, the maximum permissible dose in rem per 30 year reproductive generation, gave 1200 zygotes per million with unbalanced translocations ($1.5 \times 10^{-5} \times 2 \times 4 \times 2 \times 5 = 1.2 \times 10^{-3} = 1200 \times 10^{-6}$). A further adjustment for the 5% of these zygotes that were thought to survive, gave $1200 \times 0.05 \times 10^{-6} = 60 \times 10^{-6}$ unbalanced translocations appearing in the first generation.

By a similar calculation, survival of 5% of the offspring of the 300 zygotes per million carrying balanced translocations ($1.5 \times 10^{-5} \times 2 \times 2 \times 5 = 3 \times 10^{-4} = 300 \times 10^{-6}$), was expected to contribute an additional 15 unbalanced translocations per million to equilibrium. These values are shown in Table VII-5.

For induced aneuploidy the BEIR Committee relied exclusively on the rate of X-chromosome loss obtained from female mice (6×10^{-6} losses per gamete per rad of chronic low-LET radiation). This rate was used to estimate the frequency of viable aneuploids induced in man leading to the number 5 entered in Table VII-5.

3. Risk Relative to Current Incidence of Serious Disabilities.

The BEIR Committee also made estimates from the evidence of diseases of complex etiology, described in the Northern Ireland study (Stevenson, 1959). These diseases make up the bulk of the 56,900 cases per million live births in Table VII-5. About seventy percent of the total are congenital anomalies, anomalies expressed after birth, and constitutional and degenerative diseases. A considerable uncertainty is associated with the radiosensitive mutational component of these diseases. The mutational component, which is the proportion of the incidence that is directly proportional to the mutation rate, was estimated to lie between 5% and 50%. It was also assumed that under equilibrium conditions only 10% of the disorders would be manifest in the first generation. The values are listed in Table VII-5.

4. Risk in Terms of Ill-Health:

The BEIR Committee assumed that an independent measure of risk could be obtained from the component of ill health that results from mutationally dependent genetic disorders. It considered that perhaps 20% of all ill health had a mutationally dependent origin and therefore, by using the estimates of the doubling dose (20 rem to 200 rem), arrived at the suggestion that 5 rem per generation would increase the incidence of ill health by 0.5 to 5% (5 rem x 20%/20 rem = 5%, or 5 rem x 20%/200 rem = 0.5%).

Reconsideration of the BEIR Committee's Estimates.

Since the publication of the BEIR report, Trimble and Doughty (1974) have published a large scale study of genetically determined diseases in children in British Columbia. In the interval between the 1958 study by Stevenson and that of Trimble and Doughty, understanding of the mode of transmission of many human genetic diseases has improved considerably, and this has led to a revision of the diagnostic categories originally used in the Stevenson study. The new study showed that a larger proportion of disease--approximately 9% (instead of approximately 6%)--had a genetic basis, but that the dominant gene class was reduced. In Trimble and Doughty's study, this class was lower by an order of magnitude. Their study did not present any information on the frequency of dominant gene diseases that show late onset (i.e., become manifest after childhood) and those with variable levels of penetrance. The frequency of the last two types of dominant disease is about twice the frequency of dominant diseases measured by Doughty and Trimble. Therefore, the suggested incidence of dominant disorders is believed to be approximately 3,000 cases per million (Table VII-6) rather than the 10,000 cases per million used by the BEIR Committee (Table VII-5).

The suggestion by human geneticists that there is no mutational component associated with the diseases classified as congenital anomalies, anomalies expressed later in life, and constitutional and degenerative diseases (Newcombe, 1975) has great significance for estimating the contribution of radiation to these diseases. The argument suggests that these categories are maintained exclusively by selection mechanisms, as was described in the simple case of sickle cell anemia, and that changes in the mutation rate will not greatly affect their numbers. Under these circumstances, the radiation-induced increase will be approximately zero. The numbers in brackets in Table VII-6 would represent the contribution from a 50% mutational component. Many geneticists believe this percentage to be unrealistically high (see Newcombe, 1975). Because of this and because these numbers are not based on experimental data, less confidence should be attached to them.

Another area of reappraisal results from studies of induced chromosome aberrations. A recent analysis of translocations induced in spermatogonial cells of both humans and marmosets (primates), suggests that after 100 R of acutely delivered radiation, the frequency of translocations observed in spermatocytes is 0.077 per cell (Brewen, Preston, and Gengozian, 1975). The same authors have also demonstrated that induced translocations (Y) in mouse germ cells, as well as dicentrics in human and marmoset lymphocytes, are best related to dose (D) by a quadratic equation $Y = C + \alpha D + \beta D^2$. They calculated that for acute X-ray doses the expected frequency of transmissible translocations is between 1×10^{-4} and 2×10^{-4} translocations per gamete per rem. This calculation, however, includes both the dose and dose-squared components expected for acute high-dose irradiation and thus is likely to be too high by a factor of two when chronic low dose irradiation is considered. We shall thus assume the value per rem to be 0.5×10^{-4} to 1.0×10^{-4} transmissible translocations. The BEIR Committee's previous analysis used a rate of 3×10^{-6} (viz. $1.5 \times 10^{-6} \times 2$, the correction factor for humans). Correcting for this difference, we adopt the same approach. Thus, with exposure of 5 rem per generation, the expected number of live-born chromosomally unbalanced offspring in a million live births would be 100-200 in the first generation and 125-250 at equilibrium, (see Table VII-6.

Jacobs et al. (1972) stated that a realistic estimate of the spontaneous rate of reciprocal translocations is between 0.5 and 1.0×10^{-3} per gamete. Dividing by the radiation-induced rate obtained by Brewen, Preston, and Gengozian gives a doubling dose of 5-20 rem for this category of genetic event. Jacobs et al. (1974, p. 376) also reported data indicating that the current incidence of live-born suffering from unbalanced chromosome rearrangements is about 500 cases per million rather than 1,000 cases per million as estimated by the BEIR Committee (see Table VII-5).

Since publication of the BEIR report, data have appeared on radiation-induced nondisjunction in meiosis in the female mouse. After an average dose of 20 rad, Uchida and Lee (1974) found six oocytes out of 1,149 contained an extra chromosome. After 5 rad, only one quarter (5/20) as many will be expected. Since irradiation of males does not seem to give nondisjunction (UNSCEAR, 1972, pp. 256-257), there will be a further reduction of one half, and since the mouse has 20 pairs of chromosomes, the estimated rate per chromosome for 5 rads would then be 6/1149 x 5/20 x 1/20 x 1/2 = 32 per million. Only four types of chromosomal aneusomy have been found to be viable in humans, which leads to an estimate of 130 cases per million instead of the 5 originally given by the BEIR Committee.

A final area of reassessment involves the induced mutation rate estimates obtained from mouse studies. The BEIR Committee assumed a zero mutation rate for females based on the fact that in the mouse female the most persistent stage of oocyte (the immature stage) appears to have no mutations induced after irradiation. When the United Nations Committee (UNSCEAR, 1972, p. 252) reviewed these results they concluded that use of mutation rate estimates based on immature oocytes in the female mouse could lead to a serious error because of major differences between human and mouse oocytes both in morphology and in their response to cell killing. They felt, however, that use of risk estimates from the genetically most sensitive stage in the mouse should not result in an underestimate of the hazard to man.

Nonetheless, scientific controversy exists as to what figures should be applied here. Taken at face value, chronic irradiation of "mature" oocytes leads to a mutation rate estimate 1/20 of that obtained from acute exposure, or a rate of about 0.25×10^{-7} mutations per gene per rem ($5.4 \times 10^{-7} \times 1/20$). One recent analysis (Abrahamson and Wolff, 1976) suggests that this value might be too low since the radiation procedures lead to recovery of mouse cells that were irradiated to a substantial extent during their insensitive immature stage--a stage that may not be applicable to human risk estimates. If the latter viewpoint is shown to be correct, the risk estimate for the female is likely to be in the range of 1.2×10^{-7} mutations per rem. Since a male rate of 0.7×10^{-7} was obtained from a regression analysis of all the data from chronically irradiated spermatogonia (Searle 1974), the average for both sexes would be 1×10^{-7} rather than the value of 0.25×10^{-7} used by the BEIR Committee. This would mean that the doubling dose would be in the range of 5-50 rem for those genetic effects that are proportionally increased by irradiation. This value is used as the basis for the calculations presented in Table VII-6 even though some would argue that it is too low.

Thus, there is new evidence on the genetic basis of disease that would tend to lower the mutationally dependent contribution to future generations as well as studies and calculations that would raise the induced risk per rem of radiation for those mutationally dependent diseases. The results of combining these effects are shown in Table VII-6. Although the use of these figures can lead to a somewhat higher estimate of the genetic risk from radiation than will the use of the BEIR Committee figures, in view of the uncertainties involved, the use of the figures in Table VII-6 seems to be a responsible and prudent way to establish risks.

Somatic Effects

The somatic effects of concern at the low dose rates associated with natural background radiation are those that might conceivably result from alterations in individual cells, singly or in small numbers, in the absence of extensive cell killing or tissue disorganization. The most important such effect is considered to be the induction of cancer (BEIR Committee, 1972).

Another effect of potential concern, possibly because it may prove to have preneoplastic significance, is the induction of chromosomal abnormalities in somatic cells, the pathological importance of which is unknown at present (UNSCEAR, 1969; NAS-NRC, 1974). Other effects that are also of potential concern include infant mortality, disturbances in the growth and development of the embryo, shortening of the life span from causes other than cancer, and effects on the nervous system. To date, however, neither the available dose-response data on these effects nor our knowledge of their mechanisms suggests that they deserve to be included with cancer as risks warranting evaluation in relation to natural background radiation levels (BEIR Committee, 1972).

For the above reasons, we will confine our attention here to the possible risk of carcinogenic effects.

Radiobiological Basis For Evaluation Of Cancer Risk. As has been discussed extensively elsewhere (ICRP, 1969; BEIR Committee, 1972; UNSCEAR, 1972), there is no conclusive evidence that ionizing radiation exerts carcinogenic effects at the low dose rates commensurate with natural background. Evaluation of the potential risks at such levels must depend, therefore, on extrapolation from observations at higher doses and dose rates. Because the dose-rate characteristic of background radiation (approximately 100 mrem/year) is several orders of magnitude lower than the lowest rates at which carcinogenic effects have been documented unequivocally, the extrapolation involves assumptions that are highly tentative in our present state of knowledge.

Among the major factors complicating the extrapolation is uncertainty about the shapes of the dose-incidence curves for cancers of different types, about the relevant mechanisms of carcinogenesis, and about the influence of biological and physical variables (e.g., spatial and temporal distribution of the radiation dose, age at irradiation, sex, and physiological state) that have been observed to affect the induction of malignancy at higher dose rates in human and animal populations. The problem is further complicated by the multiplicity and diversity of effects through which radiation is thought to influence the probability of cancer development. These effects include mutagenic changes in DNA, induction of chromosomal aberrations, activation or enhancement of occult tumor viruses, alteration in the dynamics of cell populations, disturbances in hormonal regulation, impairment of immunological defenses, and other effects interfering with homeostasis. Any or all of these effects may conceivably be implicated in a given situation, depending on the dose, dose rate, and other circumstances. Some of the effects, such as disturbances in hormonal regulation and impairment of immunological defenses, are likely to be minimal or absent at low doses and low rates, since their induction requires extensive killing of cells. The other types of effects also should be reduced in frequency per rad at low doses and low dose rates, because of the action of various repair processes, at least in the case of low-LET radiation. Furthermore, if the time required to accumulate a given dose is a sufficient fraction of the life span, then, in the absence of age-dependent changes in susceptibility, the carcinogenicity per rad of the total cumulative dose can be expected to diminish, because the latent period for carcinogenesis will ultimately exceed the life expectancy of some members of the population at risk (NCRP, 1976).

Also complicating the evaluation of carcinogenic effects are the confounding effects of other forms of radiation damage. At high doses and high dose rates, the cytotoxic effects of radiation may interfere drastically with tumor induction, presumably because too few cells remain capable of proliferation to express the carcinogenic changes that might otherwise be manifest (BEIR Committee, 1972; Mole, 1975; NCRP, 1976).

For the reasons indicated, the combined effects of the various types of radiation-induced carcinogenic changes must depend heavily on the dose, dose rate, quality of radiation, and other variables; hence, it is not astonishing that the dose-incidence relationship has been observed to vary with these factors, at least in those instances where cogent data are available (BEIR Committee, 1972; UNSCEAR, 1972; NCRP, 1976). The relationship differs quantitatively, however, from one type of cancer to another, and in no instance are the parameters known well enough to enable confident prediction of the carcinogenic effects to be expected at the low dose rates associated with background radiation levels. These limitations notwithstanding, the pattern of relationships in general implies that any simple linear interpolation on dose from observations at higher doses and dose rates, without allowance for the influence of the aforementioned variables, is likely to overestimate the risks of low-level, low-LET radiation (BEIR Committee, 1972; UNSCEAR, 1972; NCRP, 1976).

It may be concluded, therefore, from all available data, that for carcinogenic effects, just as for the induction of mutations, chromosome aberrations, cell killing, teratogenic effects, and most other effects on mammalian cells and tissues, the dose-response curves for low-LET radiation will tend to be concave upward (see Fig. II-1 in Chapter II). Characteristically, the curves tend to increase in slope with increasing dose and dose rate, until they reach the point where, with high doses accumulated at high dose rates, they pass through a maximum and eventually turn downward, owing, presumably, to excessive cell killing or to other forms of injury. In comparison, the dose-response curves for high-LET radiation tend to be steeper, more nearly linear, and less dependent on dose rate (BEIR Committee, 1972; UNSCEAR, 1972; NCRP, 1976).

Because of these variations in the biological effectiveness of radiation with changes in the spatial and temporal distribution of dose, various weighting factors have been introduced for use in risk estimation. These include the quality factor (Q), which has long been used to adjust for differences in linear energy transfer, or LET (ICRP, 1963; NCRP, 1967). More recently, other dose-effectiveness factors have been introduced to adjust for the reduced effectiveness of low-LET radiation at low doses and low dose rates, both with respect to genetic effects (BEIR Committee, 1972; UNSCEAR, 1972) and carcinogenic effects (NRC, 1975; NCRP, 1976).

Although the dose-effectiveness factors for carcinogenic effects are based largely on empirical observations of radiation carcinogenesis in experimental animals, they are concordant with the data on man and with the bulk of radiobiological experience on the induction of mutations, chromosome aberrations, cell killing, cell transformation in culture, and other effects that may be involved in carcinogenesis (NCRP, 1976). The dose-response relation envisaged can be represented by a function of the form:

$$Y = (c + aD + bD^2)e^{-(\alpha D + \beta D^2)}$$

where Y is the frequency of cancers in the population at risk, c the control incidence, D the dose, and a, b, α, and β are constants. The model of carcinogenesis represented by the formula is that cancers are induced by changes that increase both linearly with dose and as the square of the dose in those cells that are not killed by radiation. The values of the constants are not known precisely for any neoplasm and they may be presumed to vary somewhat from one type of neoplasm to another and under the influence of other variables. The data imply that for low-LET radiation the linear contribution (aD) is equal to the quadratic contribution (bD^2) at about 50 to 100 rads, i.e., a/b = 50 to 100. According to this interpretation, the linear dose term (aD) would be expected to predominate over the quadratic dose term (bD^2) at low doses and low dose rates, whereas the reverse would be true at high doses and high dose rates. As a result, the carcinogenic risks per rad would be expected to increase with dose and dose rate, until overridden by excessive cell and tissue damage, the total risks per rad being as much as 4 to 6 times higher after an acutely delivered dose of 300 rads than after a dose of 10 rads (NCRP, 1976). To allow for such differences in dose-effectiveness, weighting factors have been proposed that range in magnitude from 0.2, for doses of less than 10 rads, or for larger doses received at dose rates of less than 1 millirad per minute, to 1.0 for doses of 200 rads or more received at dose rates in excess of 1 millirad/minute (Tables VII-7, VII-8).

The values tabulated have been introduced for use in estimating the overall carcinogenic risk of low-level low-LET radiation for all malignancies combined, and are not intended for use in estimating the risk per rad for every type of cancer individually, there being indications that the dose-response relation may differ among malignancies. At best, therefore, the values can be assumed to represent no more than crude approximations, based on an approach that is necessarily simplified for practical purposes. For estimating the risk of carcinogenesis in any one organ, it may be more appropriate to use other dose-response functions and weighting factors, depending on whether they may be indicated by the available data (NRC, 1975; NCRP, 1976). For example, evidence has been presented elsewhere that the dose-incidence relations for cancers of the breast and thyroid may be influenced less by dose rate (BEIR Committee, 1972; NRC, 1975; NCRP, 1976) and thus deserve to be treated differently. The values tabulated are also not intended for application to high-LET radiations, the effectiveness of which is generally assumed to be relatively invariant with dose and dose rate throughout the low-to-intermediate dose region (NCRP, 1974).

Risk Estimates for Specific Cancers. Review of the available data on human and animal populations indicated that radiation may conceivably cause cancer of virtually any type or site, given appropriate conditions of irradiation and host susceptibility (BEIR Committee, 1972; UNSCEAR, 1972). At the same time, however, the data indicate that tissues vary widely in susceptibility to radiation-induced malignancy, cancers of a relatively small number of types and sites predominating during the first 25-30 years after doses of a few hundred rems or less (ICRP, 1969; BEIR Committee, 1972; UNSCEAR, 1972).

The types of cancer that may conceivably result from low-level irradiation, the time required for their development following exposure ("latent period"), the time during which they are expected to occur in the excess among irradiated individuals ("plateau period"), and the average magnitude of the excess during the plateau period have been estimated by the BEIR Committee (1972). They assumed a linear non-threshold dose-incidence relationship fitted to the observed human data and interpolated to pass through the control incidence at the intercept (Table VII-9). In presenting the estimates tabulated, the BEIR Committee qualified the values on the basis of the following sources of uncertainty:

1. None of the irradiated human populations studied to date has been followed throughout its entire life span, with the result that the duration and ultimate magnitude of the cancer excess attributable to a given exposure remain to be fully ascertained; by the same token, it is conceivable that additional types of radiation-induced cancers with unusually long latent periods are still to become manifest.

2. The relation between the radiation-induced risk and the natural risk is not clear from the existing data; that is, it is uncertain whether the excess resulting from a given dose more nearly approximates a constant percentage of the natural incidence (and thus varies with age at time of irradiation and other susceptibility factors) or a constant number of additional cases (irrespective of the natural incidence).

3. The existence of various kinds of homeostatic and repair processes argues strongly that the risk per rad of background radiation is likely to be smaller than that at the higher doses and dose rates where effects have been observed; in fact, the possibility that the risk may approach zero at background levels is not excluded by the data.

4. The killing of susceptible cells at high doses and high dose rates can be expected to counteract the carcinogenic effects of radiation to some extent, with the result that linear extrapolation based on effects observed under these circumstances may, conceivably, underestimate the risk of irradiation at lower doses and dose rates (BEIR Committee, 1972).

Although the values tabulated (Table VII-9) may ultimately prove to be underestimates, for the reasons given above, most observers have considered them more likely to be overestimates, owing to their failure to make any allowance for the effects of repair at low doses and dose rates, effects that have been amply documented in experimental animals. Thus, more recent evaluations of the risks of low-level low-LET irradiation have recommended the use of the aforementioned dose-effectiveness factors (Tables VII-7, VII-8) in arriving at estimates for low doses and low dose rates by extrapolation from observations at higher doses and higher dose rates (NRC, 1975; NCRP, 1976).

In the Reactor Safety Study (NRC, 1975), while the upper bound estimates were derived from absolute risk values obtained by the BEIR Committee, the central estimates (Table VII-10) were small fractions of these values, derived by the use of dose-effectiveness factors (Table VII-8) intended to correct the estimates for the influence of repair at low doses and low dose rates of low-LET radiation. The lower bound estimates were based on the assumption that below a threshold of 10-25 rem the risk per rad was zero.

The dose-effectiveness factors proposed by NCRP Scientific Committee 40 (Table VII-7) are similar in direction and range to those used in the Reactor Safety Study, but they differ in magnitude at low doses, especially over the region between 10 and 100 rads. Because of this difference, and the fact that most of the human data on radiation carcinogenesis come from populations in which the average dose received in any one exposure has not greatly exceeded 100 rads, estimates derived with the NCRP factors should be intermediate between those calculated in the Reactor Safety Study and those reported by the BEIR Committee (Table VII-11). From the values tabulated, it will be noted that the number of cancers attributed hypothetically to continuous low-level irradiation of the U.S. population at a rate approximating natural background radiation levels (100 mrem per year) ranges from 0 to roughly 9,000 depending on the method used to arrive at the risk estimate. The larger of the values (9,000) corresponds to about 2.9% of the total number of cancer deaths from all causes recorded annually in the U.S. (BEIR Committee, 1972).

The enormous variation among estimates yielded by different extrapolation models (Table VII-11) reflects the large uncertainty about dose-response relationships that complicates current attempts to estimate the carcinogenic risks of low-level irradiation. The criteria for selecting one method of risk estimation in preference to another must thus depend in large measure on other than purely scientific considerations. To the extent that the estimates are intended for purposes of limiting risks to populations, it is desirable that they should include a margin of safety large enough to compensate for any uncertainty as to their reliability. On the other hand, if the estimates are to be used for purposes of cost-benefit analysis, it is desirable that they not be exaggerated, since over-estimation of the risks may prompt decisions in favor of alternatives that could involve greater hazards or burdens to society.

RISKS FROM RADIOACTIVE DRINKING WATER

The average amount of background radiation to which the U.S. population is exposed is about 0.1 of a rem (100 mrem) per year. Part of this background comes from drinking water that contains radioactive materials.

The dose commitment from radioisotopes in U.S. drinking water supplies is very low. In a hypothetical water supply that was constituted in such a way as to contain either average or likely amounts of radioactivity, a total-body dose of less than one-thousandth of a rem (0.244 mrem) per year would be accumulated. This is less than 1% of background. Although the dose to bone would be considerably higher, because strontium and radium are bone-seekers, even this dose would constitute less than 10% of the total average natural background.

Estimates were made of three possible types of risk that could be induced by the radiation: developmental and teratogenic risks, genetic risks, and somatic risks.

Developmental and Teratogenic Risks

Although the developing fetus is sensitive to radiation, the total low-dose-rate doses that would be delivered during the sensitive periods of gestation, are so low that no measurable effects of the radiation from drinking water will be found. The lowest dose levels at which any effect has been reported is 3 mrem/day or 1100 mrem/year in contrast to the 0.244 mrem per year described above.

Genetic Risks.

For the general population, the maximum permissible dose of man-made radiation is 170 mrem/year, excluding medical uses of radiation. This amounts to a 5 rem genetic dose in each 30 year generation. This dose would increase the current incidence of genetic diseases, which is about 94,000 per million live births, by about 200 per million in the first generation. The estimate of 200, however, is so uncertain that there are very large limits about the value. The gonadal dose of 0.244 mrem/year calculated for the hypothetical drinking water is expected to increase the genetic diseases from the 94,000/10^6 live births by 200 x 0.244 mrem/30 x 170 mrem = 0.0098 additional genetic diseases per million live births per year. Since there are approximately 3.6 million live births in the U.S. each year, this is an increase of 0.035 total genetic diseases in the U.S. per year. If one takes the unlikely extreme limits of the estimated genetic hazards of radiation (about 4,000) instead of the value 200, the increase is 0.7 cases per year.

Somatic Risks

The natural background of radiation can be estimated to cause 4.5 to 45 fatal cases of cancer per year per million people, depending on the risk model used to make the calcu[illegible] (Table VII-11). Less than 1% of this will be contributed by the radionuclides in drinking water.

Variations in the radium content of drinking water, however, may cause appreciable differences in the radiation dose to the skeleton and, in turn, in the risks of associated carcinogenic effects. Under average conditions, the annual dose to bone from radium amounts to approximately 6.4 mrem/year, which represents about 6% of the total dose to the skeleton from all sources of natural background radiation (roughly 100 mrem annually). The highest radium levels in drinking water (25 pCi/liter of ^{226}Ra and an additional 12.5 pCi/liter of ^{228}Ra), however, may be expected to deliver a dose to the skeleton of about 600 mrem per year, which would represent a 6-fold increase in the total dose to bone from all natural sources combined. If the carcinogenic risks associated with skeletal irradiation are assumed to be 0.2 fatal cases of bone cancer per million persons per year per rem (Table VII-9), then for a period up to 30 years, in a population with a typical distribution of ages, the risks attributable to natural background radiation can be estimated to range up to about 0.6 per million persons per year under average conditions,*

$$^*\frac{0.2\ \text{fatal cases} \times 0.1\ \text{rem/yr} \times 30\ \text{yrs}}{10^6\ \text{persons per yr per rem}} = 0.6\ \text{fatal cases per } 10^6\ \text{persons per year}$$

and to 4.2 per million per year under conditions of maximal intake of radium in the drinking water (about 600 mrem per year from the radium).

In addition to these risks, the possibility of carcinogenic effects from radium on cells adjacent to bone, such as those in epithelia lining cranial sinuses and those in the bone marrow, should also be mentioned; however, the risks of such effects are likely to be appreciably smaller and cannot be estimated precisely from existing data. In comparison with the overall risks of cancers of all sites combined, of which 4.5 to 45 (i.e. 9000/200) fatal cases per million per year can be attributed to natural background radiation at average levels (Table VII-11), the additional 1.6 fatal bone malignancies per million per year ascribable to maximal intakes of radium in drinking water constitute a significant increment. It should be noted that only about 120,000 people drink water estimated to contain between 9 and 25 pCi/liter. Thus the excess bone cancers in this group would be between 0.16 and 0.43 per year; that is to say, one excess bone cancer every two to six years. Since about 113,000 of the 120,000 people drink water containing less than 20 pCi/liter, the true number of excess bone cancers will lie somewhere towards the lower end of the range.

When interpreting the above estimates, it must be remembered that they depend on dose-response models that remain highly uncertain. For example, the value given for the combined frequency of deaths from all types of cancer attributable to natural background radiation-- namely, 45 deaths per million per year-- is higher by a factor of three or more than estimates derived with any of the other risk models cited (Table VII-11). Likewise, the corresponding risk estimates for skeletal cancer could vary widely, depending on the postulated dose-response relationship. Although the value yielded by the BEIR Committee's absolute risk model (0.2 fatal cancers per million per year per rem) is not greatly different from the value yielded by the BEIR Committee's relative risk model (since 9 out of the 1,704 fatal cancers per million per year are bone cancers, this would be approximately 0.09 fatal bone cancers per million per year per rem), both models, in postulating a linear nonthreshold dose-response relationship, give substantially higher estimates than do models postulating dose-dependent and dose-rate-dependent variations in the risk per rem. Given the uncertainties in present knowledge, the BEIR Committee's absolute risk model as used in the foregoing would seem to provide an acceptably conservative approach for the purposes at hand.

SUMMARY

Everyone is exposed to some natural radiation that comes from both cosmic rays and terrestrial sources. Although there are large geographic variations in the amount of natural background radiation, the average background dose in the United States is about 100 mrem/year. A small proportion of this unavoidable background radiation comes from drinking water that contains radionuclides.

By far the largest contribution to the radioactivity in drinking water comes from potassium-40, which is present as a constant percentage of total potassium. Only a small percentage of the total potassium-40 body burden, however, comes from drinking water. The total body dose from other possible radioactive contaminants of water constitutes a small percentage of the background radiation to which the population is exposed. Although the amounts of individual radioactive contaminants fluctuate from place to place, calculations made for a hypothetical water supply that might be typical for the United States have shown that a total soft-tissue dose of only 0.28 mrem/year would be contributed by all the radionuclides found in the water. Even with rather wide fluctuations in the concentrations, the total contribution of the radionuclides will remain very small.

However, bone-seeking radionuclides--such as strontium-90, radium-226, and radium-228--account for a somewhat larger proportion of the total bone dose. This is particularly true for the two isotopes of radium because they emit high-linear-energy-transfer (LET) radiation, and because certain restricted localities have been found to have rather high concentrations of radium in drinking water. Nevertheless, in the hypothetical typical water supply, less than 10% of the annual background dose comes from such radiation. It has also been estimated that the total population exposed to levels of radium greater than 3 pCi/liter is about a million people. About 120,000 people are exposed to radium at levels greater than 9 pCi/liter.

Risk estimates were made of three kinds of adverse health effects that radiation could produce: developmental and teratogenic effects, genetic effects, and somatic (chiefly carcinogenic) effects.

Developmental and Teratogenic Effects

The developing fetus is exposed to radiation from radionuclides in drinking water for nine months. Thus, the total dose accumulated by the fetus will be very small. Furthermore, although the fetus is sensitive to the effects of radiation in some stages of development, these periods are sharply limited and extremely short. For this reason, too, the total dose administered that could have possible developmental and teratogenic effects would be extremely small. Current concentrations of radionuclides in drinking water lead to doses of about one five-thousandth of the lowest dose at which a developmental effect has been found in animals. Therefore, the developmental and teratogenic effects of radionuclides would not be measurable.

Genetic Effects

It has been estimated that there are about 94,400 genetic diseases per million live births in the United States. The maximum permissible dose of man-made radiation for the general population (170 mrem/year) has been estimated to increase this number in the first generation by 170-215, with an unlikely upper limit of 4,250. On the basis of a 30-year generation and 3.6 million live births per year in the United States, we would expect the 0.28 mrem soft-tissue dose, or gonad dose, to lead to 0.0098 additional cases of genetic disease per million live births per year or 0.035 additional cases of genetic disease in the United States per year. Even at the unlikely extreme upper limit of possible genetic effects of radiation of around 4,000 extra cases in the first generation, there would still be less than one additional case in the 94,400 x 3.6 = 340,000 live births with genetic defects. The wide fluctuation in bone dose caused by fluctuations in the radium concentration of drinking water would not have any sensible effect on the genetically significant dose, because radium is predominantly a bone-seeker and will deliver very little radiation to the gonads.

Somatic and Carcinogenic Effects

The natural background of radiation can be estimated to cause 4.5 to 45 cases of cancer per million people, depending on the risk model used. The amount of whole-body radiation from radionuclides in typical drinking water contributes less than 1% of this amount, and thus, for cancers other than those in bone, may cause a negligible increase in the total. Radium, however, can contribute somewhat less than 7% of the total bone dose received from background radiation in areas of "normal" radium concentration. The average carcinogenic risk associated with skeletal irradiation by radium in a population with a typical distribution of ages, is estimated to approximate 0.2 fatal cases of bone cancer per million persons per year per rem. Therefore, over a period from 10 to 40 years after the beginning of skeletal irradiation, the average risk attributable to natural background radiation is estimated to range from 0.6 per million persons per year, under typical conditions, to as much as 4.2 per million per year, in regions where 25 pCi/liter of radium-226 are found in the drinking water. It has been noted that in the United States 120,000 people are estimated to drink water containing between 9 and 25 pCi/liter of radium-226 and only a small number lie near the upper end of this range. The number of excess cancers in this group would therefore lie between 0.16 and 0.41 per year. Since not all the 120,000 people drink water containing 25 pCi/liter of radium-226, the latter number is inordinately high.

CONCLUSIONS

The radiation associated with most water supplies is such a small proportion of the normal background to which all human beings are exposed, that it is difficult, if not impossible, to measure any adverse health effects with certainty. In a few water supplies, however, radium can reach concentrations that pose a higher risk of bone cancer for the people exposed.

FUTURE NEEDS

The precision of estimation of the health risks associated with radioactivity in drinking water could be enhanced if several water systems were analyzed to determine the complete distributions of beta and alpha radiation that constitute the gross counting measurements.

Because the precise ratio of radium-228 to radium-226 in water has not been measured extensively, an attempt should be made to determine the ratio in several ground and surface waters whose content of radium-226 is known. The waters to be analyzed should range from about 0.1-50 pCi/liter. The percentage of the daughter radionuclides present should be determined.

Because radon is a noble gas that is quickly released from water, it is possible that, in some areas of high radon content, water vapor containing radon might constitute an inhalation hazard when such water is used, for example, in humidifiers or for showers. A determination should be made whether or not radon emanations from water do indeed constitute an inhalation hazard.

The models used in this report do not take into account the possibility that the finely divided solid particles that occur in water may alter the uptake of radionuclides. The effects of the solids in drinking water on the metabolism and uptake of radionuclides merit investigation.

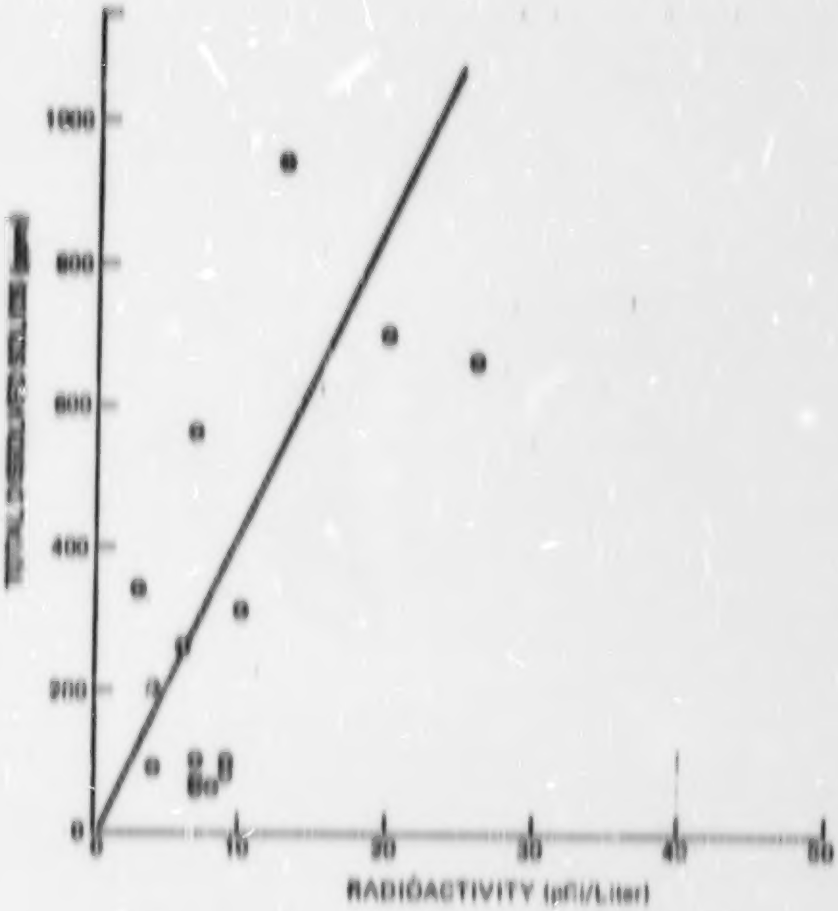

Figure VII-1. Relationship between total dissolved solids and radioactivity of California domestic water (Goldberg 1976).

TABLE VII-1. Estimated total annual whole body doses from natural radiation in the United States (From BEIR Committee, 1972).

Source	Annual Doses mrem
Cosmic Rays	44
Terrestrial Radiation	
External	40
Internal	18
Total	102

Table VII-2. Adult Equilibrium Annual Dose Factors for Some Radionuclides in Water

(Based on NCRP Report No. 22 (1963 rev.), Soldat et al. 1974, and alkaline earth values as described in text).

	MILLIREM PER YEAR IN YEAR 50 OF CONSTANT INTAKE AT				
	1 pCi per year			1 pCi per 1.2 l per day	
Nuclide	Total Body	Organ Specific	Organ	Total Body	Organ Specific
^{3}H	1.1×10^{-7}	-		8.9×10^{-5}	-
^{14}C	5.7×10^{-7}	-		4.2×10^{-4}	-
^{40}K	3.4×10^{-5}	-		2.0×10^{-2}	-
^{54}Mn	8.7×10^{-7}	1.4×10^{-5}	GI (LLI)	6.4×10^{-4}	1.0×10^{-2}
^{87}Rb	4.3×10^{-6}	-		3.1×10^{-3}	-
^{89}Sr	5.6×10^{-7}*	7.1×10^{-5}	Bone	4.1×10^{-4}*	5.2×10^{-2}
^{90}Sr+D	3.2×10^{-6}*	6.3×10^{-3}	Bone	2.3×10^{-3}*	4.6×10^{0}
^{95}Zr+D	6.6×10^{-9}	3.0×10^{-5}	GI (LLI)	4.8×10^{-6}	2.0×10^{-2}
^{99m}Tc	8.9×10^{-9}	4.1×10^{-7}	GI (LLI)	6.5×10^{-6}	3.0×10^{-4}
^{129}I	9.2×10^{-6}	7.2×10^{-3}	Thyroid	6.7×10^{-3}	5.3×10^{0}
^{131}I+D	3.4×10^{-6}	1.9×10^{-3}	Thyroid	2.5×10^{-3}	1.4×10^{0}
^{134}Cs	1.2×10^{-4}	-		8.9×10^{-2}	-
^{137}Cs+D	7.1×10^{-5}	-		5.2×10^{-2}	-
^{144}Ce+D	2.6×10^{-8}	1.7×10^{-4}	GI (LLI)	1.9×10^{-5}	1.2×10^{-1}
^{210}Pb+D	5.4×10^{-4}	1.2×10^{-2}	Kidney	3.9×10^{-1}	9.0×10^{0}
^{210}Po	8.6×10^{-5}	2.5×10^{-3}	Kidney	6.3×10^{-2}	1.8×10^{0}
^{226}Ra+D	8.7×10^{-4}*	2.2×10^{-2}	Bone	2.7×10^{-1}*	1.6×10^{1}
^{228}Ra+D	8.1×10^{-4}*	2.2×10^{-2}	Bone	5.9×10^{-1}*	1.6×10^{1}
^{232}Th+D	4.9×10^{-5}	1.8×10^{-3}	Bone	3.6×10^{-2}	1.3×10^{0}
^{238}U+D	4.5×10^{-5}	7.7×10^{-4}	Bone	3.3×10^{-2}	5.6×10^{-1}
^{239}Pu	1.9×10^{-5}	7.9×10^{-4}	Bone	1.0×10^{-2}	5.8×10^{-1}

*Values are soft tissue doses, not total body doses.

Factors in left-hand columns also give total dose accumulated over 50 years after a single acute intake, by an adult, of 1 pCi.

TABLE VII-3. Activity in a hypothetical water supply.

Nuclide	Concentration pCi/liter	Potential Doses (mrem/yr) Total Body	Bone Dose
Beta Activity			
^{3}H	250	0.02	-
^{40}K	2.2	0.046	-
^{90}Sr	0.5	0.001	2.3
^{137}Cs	0.1	0.005	-
^{228}Ra	0.3	-	-
Total Beta	3.1 (less ^{3}H)	0.072	2.3
Alpha Activity			
^{226}Ra & daughters	0.2	0.054	3.2
^{228}Ra & daughters	0.2	0.118	3.2
Total Alpha	0.4	0.172	6.4
Grand Total		0.244	8.7

TABLE VII-4. Some selected types of human diseases caused by "mutation".

Dominant
  Neurofibromatosis
  Chondrodystrophy
  Hereditary chorea
  Congenital cataract
  Osteogenesis imperfecta

Sex-linked
  Hemophilia A & B
  Progressive muscular dystrophy
  Hypogammaglobulinemia
Recessive
  Cystic fibrosis
  Phenylketonuria
  Amaurotic idiocy
  Cystic kidney disease
  Albinism
  Deafness

Chromosomal
  Down's syndrome
  Edwards' syndrome
  Patau's syndrome
  Sex chromosome anomalies
  Cri du chat syndrome

Multifactorial
  Diabetes mellitus
  Idiopathic mental retardation
  Myopia
  Asthma
  Schizophrenia, several types
  Epilepsy, several types
  Strabismus, convergent

Table VII-5, Estimated effects of 5 rem per generation on a population of one million live births. Figures from BEIR Committee (1972).

Disease Classification	Current Incidence	Effect of 5 rem per generation First Generation	 Equilibrium	Generations to Equilibrium
Dominant diseases	10,000	50-500*	250-2500	5
X-linked recessive diseases	400	0-15*	10-100	6
Recessive diseases	1,500	very few	very slow increase	
Chromosomal anomalies				
Unbalanced rearrangements	1,000	60	75	2-3
Aneuploidy	4,000	5	5	0
Congenital anomalies	15,000			
Anomalies expressed later	10,000	5-500	50-5000	10
Constitutional and degenerative diseases	15,000			
Total	56,900	120-1100	390-7700	

*Based on a doubling dose of 20-200 rem.

Table VII-6. Estimated effect of 5 rem per generation on a population of one million live births. BEIR Committee estimates modified to account for new data and approaches.

Disease Classification	Incidence	Effect of 5 rem per generation First Generation	Equilibrium
Dominant diseases	3,000	60-600*	300-3,000*
X-linked recessive diseases	400	7-70*	40-400*
Recessive diseases	1,500	very few	very slow to increase
Chromosomal anomalies			
Unbalanced rearrangements	500	100-200	125-250
Aneuploidy	4,000	5-130	5-130
Congenital Anomalies			
Anomalies expressed later	85,000	(0-43)-[4,250]#*	(0-425)-[42,500]#*
Constitutional and degenerative diseases			
TOTAL	94,400	(172-215)-[5,250]#	(474-900-[46,300]#

*based on a doubling dose of 5-50 rem.

#the numbers in brackets are likely to be unreasonably high (see text).

TABLE VII-7. Dose-effectiveness factors for carcinogenic effects of low-LET radiation, in relation to dose rate and dose magnitude, as proposed by NCRP, Scientific Committee 40 (NCRP, 1978)

Yearly Dose rad	Effect-to-Dose Ratio At < 1 mrad/min	 At > 1 mrad/min
0 - 5	0.2	0.2
5 - 50	0.2	0.3
50 - 100	0.2	0.5
100 - 200	0.2	0.7
200+	0.2	1.0

The values tabulated represent the assumed comparative effectiveness per rad of low-LET radiation in the ranges of dose and dose-rate indicated, for purpose of risk estimation.

TABLE VII-8. Dose-effectiveness factors for carcinogenic effects of low-LET radiation, as used in the Reactor Safety Study, (NRC, 1975).

Total Dose rem	at <1 rem/day	Effect-to-Dose Ratio at 1-10 rem/day	at > 10 rem/day
10	0.2	0.2	0.2
10 - 25	0.2	0.4	0.4
25 -100	0.2	0.4	1.0

Table VII-9. Values assumed by BEIR Committee (1972) in estimating risks of low level irradiation.

Type of Cancer	Age at Time of Irradiation (years)	Latent Period (years)	Plateau Period (years)	Risk Estimate: Absolute (deaths/10^6/yr/rem)	Risk Estimate: Relative (% incr. in deaths/rem)
Leukemia	*In utero*	0	10	25	50
"	0-9.9	2	25	2	5.0
"	10+	2	25	1	2.0
Lung	10+	15	30(a)	1.3	0.3
GI tract, including stomach	10+	15	30(a)	1.0	0.2
Breast	10+	15	30(a)	1.5(b)	0.6
Bone	10+	15	30(a)	0.2	1.0
All other(c)	*In utero*	0	10	25(d)	50
"	0-9.9	15	30(a)	1(d)	2.0
"	10	15	30(a)	1(e)	0.1

(a) Alternatively, the remaining life expectancy could be considered as the plateau period.

(b) Includes males and an assumed 50% cure rate.

(c) Includes thyroid and skin. It is noteworthy that the mortality from thyroid cancer was inferred to be low, as compared with the morbidity from the disease, which was estimated to approximate 1.6-9.3 cases/10^6/yr/rem in persons irradiated during childhood.

(d) "All other" denotes all cancers except leukemia.

(e) "All other" denotes all cancers except those specified in table.

Table VII-10. Values assumed in Reactor Safety Study for use in estimating risks of low level low LET irradiation (NRC, 1975).

Type of Cancer	Age at Time of Irradiation (years)	Latent Period (years)	Plateau Period (years)	Risk Estimate	
				Bound (deaths/10^6/yr/rem)	Estimate (deaths/10^6/yr/rem)
Leukemia	In utero	0	10	15	3
"	0-9.9	2	25	2	0.4
"	10+	2	25	1	0.2
Lung	10+	15	30	1.3	0.3
Stomach	10+	15	30	0.6	0.12
Rest of GI tract	10+	10	30	0.2	0.04
Pancreas	10+	15	30	0.2	0.04
Breast	10+	15	30	1.5(a)	1.5
Bone	0-19.9	10	30	0.4	0.08
"	20+	10	30	0.2	0.04
All other	In utero	0	10	15(b)	3
"	0-9.9	15	30	0.6(c)	0.12
"	10+	15	30	1(d)	0.2

(a) Includes males and an assumed 50% cure rate.

(b) "All other" includes all cancers except leukemia.

(c) "All other" includes all cancers except leukemia and bone.

(d) "All other" includes all cancers except those specified in table.

Table VII-11. Comparative estimates of the number of cancer deaths per year in the U.S. population attributable to continuous exposure at rate of 0.1 rem per year.

Age at Time of Irradiation	Duration of Plateau Period (years)	Estimated Excess Cancer Deaths Resulting from 0.1 Rem per Year[a]						
		BEIR Estimates[b]		NRC Estimates[c]			NCRP Estimates[d]	
		(Absolute Risk Model)	(Relative Risk Model)	(Upper Bound)	(Central Estimates)	(Lower Bound)	(Absolute Risk Model)	(Relative Risk Model)
In utero	10	150	110	90	20	0	150	110
0-9 years	25-30	260	800	240	80	0	100	320
	life	290	6000	*	*	*	120	2400
10+ years	25-30	1300	2200	1300	500	0	520	880
	life	1600	3000	*	*	*	640	1200
Total	25-30	1700	3100	1630	600	0	770	1310
	life	2000	9000	*	*	*	910	3710

(a) Values in Table have been rounded to facilitate comparison.

(b) From BEIR Committee 1972, p. 169, based on vital statistics for U.S. population, 1967.

(c) Values are rough calculations, based on application of NRC (1975) risk models to U.S. population, 1967.

(d) Values are rough calculations, based on application of NCRP (1975) risk model to U.S. Population, 1967. The values for irradiation *in utero* are the same as the BEIR Committee's estimates, without adjustment for dose or dose rate, since they are based on data from populations exposed to doses averaging 5 rads or less. The values for postnatal irradiation, on the other hand, have been derived by adjusting the BEIR estimates for dose and dose rate by application of the appropriate dose-effectiveness factors set forth in Table VII-7. Since the BEIR Committee's estimates are based largely on data from populations in which the average dose received in any one exposure did not greatly exceed 100 rads, and a dose rate corresponding to a dose-effectiveness factor of 0.5 (Table VII-7), the BEIR values have been multiplied by a factor of 0.2/0.5 to adjust them for the conditions of low-dose low-dose-rate irradiation in question.

GLOSSARY

Absolute risk. Excess or incremental risk due to exposure to a toxic or injurious agent (e.g. to radiation). Difference between the risk (or incidence) of disease or death in the exposed population, and the risk in the unexposed population. Usually expressed as number of excess cases in a population of a given size, per unit time, per unit dose (e.g. cases/10^6 exposed population/year/rem).

Curie (Ci). Unit of radioactivity. 1 Curie = 3.7×10^{10} nuclear transformations per second. Common fractions are: millicurie (1 mCi = 10^{-3}Ci), microcurie (1 μCi = 10^{-6}Ci), nanocurie (1 nCi = 10^{-9}Ci), picocurie (1 pCi = 10^{-12}Ci), femtocurie (1 fCi = 10^{-15}Ci).

Latent period. Period between time of exposure to a toxic or injurious agent and appearance of a biological response.

LET. Linear energy transfer. Average amount of energy lost by an ionizing particle or photon per unit length of track in matter.

Plateau period. Period of above-normal, relatively uniform, incidence of disease or death in response to a toxic or injurious agent.

Rad. Unit of dose or radiation (energy) absorbed in any medium, except air. 1 rad = 100 erg/g.

Relative risk. Ratio of the risk in the exposed population to that in the unexposed population. Usually given as a multiple of the natural risk.

Rem. Unit of radiation dose equivalence. Numerically equal to absorbed dose in rad multiplied by a quality factor that expresses the biological effectiveness of the radiation of interest, and other factors. Equal doses expressed in rem produce the same biological effects, independently of the type of radiation involved.

Roentgen (R). Unit of radiation (energy) absorbed in air. 1 R = 2.58×10^{-4} coulomb/kg of air.

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APPENDIX A

Legislation and Terms of Reference of the Study

The Safe Drinking Water Act of 1974 and the NAS Study

(Public Law 93-523)

Purpose of legislation

The purpose of the legislation is to assure that the public is provided with an adequate quantity of safe drinking water. It is to assure that water supply systems serving the public meet minimum national standards for protection of public health.

Until passage of the Act, the Federal Government was authorized to prescribe drinking water standards only for water supplies used by interstate carriers, and they were enforceable only with respect to contaminants capable of causing communicable diseases. Public Law 93-523 authorized the Environmental Protection Agency to establish Federal standards for protection from all harmful contaminants and established a joint Federal-State system for assuring compliance with these standards and for protecting underground sources of drinking water.

Abridged summary of the legislation

a. Required the Administrator of EPA to prescribe national drinking water regulations for contaminants which may adversely affect health.

b. Provided that such regulations apply to public water systems and protect health to the maximum extent feasible.

c. Provided that interim primary regulations be prescribed initially and that, after a study by the National Academy of Sciences, health goals were to be established and revised primary regulaions promulgated. That portion of the Act pertaining to the NAS study and the scope of work is detailed below.

d. Provided for a number of other requirements and administrative authorizations not directly related to the NAS study.

Need for legislation

Congressional hearings, EPA studies, and evidence from a number of sources established that legislative authority prior to passage of the Act was inadequate to assure that water supplied to the public was safe to drink.

This conclusion was based on evidence that waterborne disease outbreaks still occur in this country. Examples include an epidemic at Riverside, California in 1965 that affected 18,000 people, an outbreak of gastroenteritis in Angola, New York in 1965 affecting 30% of the population and an epidem[illegible] of giardiasis in Rome, New York in 1974 affecting alm[illegible] 5,000 people. According to a 1970 EPA survey of 969 dri[illegible]ng water supply systems, approximately 8 million people in this country are served water that is potentially dangerous in that it failed to meet the mandatory standards set by the Federal Government with respect to interstate carrier systems. The deficiencies in the majority of cases were in smaller systems.

Until passage of the Act there was no provision in Federal law to protect the public from chemical poisoning and none to protect those not traveling on interstate conveyances from being supplied with drinking water which may cause communicable or noncommunicable illness.

Several extensive surveys have shown serious deficiencies in the number f water samples examined and in the bacteriological and chemical quality of drinking water. Many systems had physical deficiencies including poorly protected groundwater sources, inadequate disinfection and clarification capacity. In addition, plant operators were inadequately trained. Plants were not being inspected by State or local authorities. In one survey, 50 percent of plant officials did rot remember when, if ever, they had been surveyed by a State or local health department.

House of Representatives Report No. 93-1185 and Senate Report No. 93-231 and Public Law 93-523 are the sources of information for the foregoing.

The National Academy of Sciences Study

Public Law 93-523 (Section 1412(e)) mandated the NAS study as follows:

1. The Administrator shall enter into appropriate arrangements with the National Academy of Sciences (or with another independent scientific organization if appropriate arrangements cannot be made with such Academy) to conduct a study to determine:

   A. The maximum contaminant levels which should be recommended in order to protect the health of persons from any known or anticipated adverse effects, and from any known or anticipated adverse effects, and
   B. The existence of any contaminants the levels of which in drinking water cannot be determined but which may have an adverse effect on the health of persons.

2. The result of the study shall be reported to Congress no later than 2 years after the date of enactment of this title. The report shall contain:

   A. A summary and evaluation of relevant publications and unpublished studies;
   B. A statement of methodologies and assumptions for estimating the levels at which adverse health effects may occur;
   C. A statement of methodologies and assumptions for estimating the margin of safety which should be incorporated in the national primary drinking water regulations;
   D. Proposals for recommended maximum contaminant levels for national primary drinking water regulations;
   E. A list of contaminants the level of which in drinking water cannot be determined but which may have an adverse effect on the health of persons; and
   F. Recommended studies and test protocols for future research on the health effects of drinking wter contaminants, including a list f the major research priorities and estimated costs necessary to conduct such priority research.

3. In developing its proposals for recommended maximum contaminants levels, the National Academy of Sciences shall evaluate and explain the impact of the following considerations:

   A. The existence of groups or individuals in the population which are more susceptible to adverse effects than the normal healthy adult.
   B. The exposure to contaminants in other media than drinking water (including exposures in food, in the ambient air, and in occupational settings) and the resulting body burden of contaminants.
   C. Synergistic effects resulting from exposure to or interaction by two or more contaminants.

   D. The contaminant exposure and body burden levels which alter physiological function or structure in a manner reasonably suspected of increasing the risk of illness.

4. In making the study under this subsection, the National Academy of Sciences (or other organization) shall collect and correlate:

   A: Morbidity and mortality data and
   B: Monitored data on the quality of drinking water. Any conclusions based on such correlation shall be included in the report of the study.

5. Neither the report of the study under this subsection nor any draft of such report shall be submitted to the office of

Management and Budget or to any other Federal agency (other than the Environmental Protection Agency) prior to its submission to Congress.

6. Of the funds authorized to be appropriated to the Administrator by this title, such amounts as may be required shall be available to carry out the study and make the report.

Scope of Work

Thus further definition of the scope of work was developed jointly between NAS and EPA.

The Academy will undertake to complete the study and report described in Section 1412(e) of the Public Health Service Act, as amended by the Safe Drinking Water Act, with the following understanding: The Academy considers that the intent of Congress in using the phrase "maximum contaminant levels which should be recommended ... in order to protect the health of persons from any known or anticipated adverse effects" is to provide for recommendations that are consistent with the best scientific knowledge. It is the Academy's judgement that from a scientific point of view, the absolute guarantee of safety implied by this language cannot be made for most or all of the contaminants to be studied. The Academy report will explain and discuss this point. Accordingly, with respect to recommended levels, taking only health effects into account, the Academy's report will provide the following:

(1) Where there are sufficient data from which a human dose-response relationship can be projected with some degree of precision, a projection will be made. The projection will be explained and its qualifications will be made explicit.

(2) For contaminants for which the data are of sufficient quantity and quality, the Academy will exercise its scientific judgement and identify and propose contaminant levels for which it anticipates the risk of adverse health effects to be specifiable and very small. The risks at the proposed levels will be described, with an explanation as to why no "safe" level has been identified.

(3) For contaminants for which the evidence provides no scientific basis or methodology for recommending levels, the Academy will describe the available data, and its significance in terms of known or anticipated adverse health effects.

APPENDIX B

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